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FEDERAL SECURITY AGENCY
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

DIVISION OF RESEARCH GRANTS AND FELLOWSHIPS

ANNUAL REPORTS

of the

STUDY SECTIONS

August 25, 1948

FEDERAL SECURITY AGENCY
PUBLIC HEALTH SERVICE
U.S. NATIONAL INSTITUTES OF HEALTH

DIVISION OF RESEARCH GRANTS AND FELLOWSHIPS

ANNUAL REPORTS
of the
STUDY SECTIONS

August 23, 1948

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PREFACE

I should like to take this opportunity to express to the members of the special Study Sections of the National Institutes of Health the appreciation of the Division of Research Grants and Fellowships for the cooperation received in preparation of annual reports for fiscal year 1948.

These reports, presented in the following pages, are being transmitted to each Study Section and National Advisory Health Council member. It is hoped that the reports will be of value as a source of information and of service in the overall planning of Study Section activities.

These annual reports have been of invaluable assistance to the Division of Research Grants and Fellowships in planning for the future of the research grants program.

D E Price

David E. Price, M.D., Dr. P.H.
Chief, Division of Research
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ANTIBIOTICS STUDY SECTION

June 30, 1948

ANTIBIOTICS STUDY SECTION

I. PROGRESS IN RESEARCH.

A. Overall Progress

Largely as a result of stimulation provided through the Antibiotics Study Section, satisfactory progress has during the past year been achieved in pilot studies in clinical evaluation urgently required for the direction of investigations of the efficacy of specific antibiotics in various diseases, such as bacillary enteritis, whooping cough, and pneumonias of bacterial origin.

Enlightening results have been obtained on such diverse topics as the protective effect of penicillin against bacterial endotoxins, the role of immunity in recovery from antibiotic-treated infections, and the interaction of blood proteins with antibiotics. In a broad sense, the last year has resulted in a better understanding of the relative values of the individual penicillins; the further delineation of the efficacy streptomycin; advances in the clinical knowledge regarding bacitracin; the clinical and experimental introduction of the polymyxin-aerosporin antibiotics which promise to be effective against brucellosis and analogous conditions.

B. Progress in Specific Projects.

In individual projects directly supported by the U. S. Public Health Service grants-in-aid program, a considerable amount of information has been gathered on bacterial resistance to antibiotics; the possible role of antibiotics of the penicillin group in protein-binding and other surface phenomena; the effect of antibiotics on the normal immunity mechanisms of the host.

A chemical method for the estimation of streptomycin in biological fluids and tissues has been developed, and progress is being made on chemical methods for assaying other antibacterial agents. Intensive investigations have been conducted to learn the efficacy of the more commonly known antibiotics against whooping cough and neonatal and childhood diarrheas, and similar efforts are being made with the newer, more promising antibiotic substances.

II. RESUME OF STUDY SECTION ACTIONS ON APPLICATIONS FOR RESEARCH GRANTS (January 1, 1946, to July 1, 1948).

A. Number of applications considered: 68, in amount of $550,697.
B. Number of applications approved: 48, in amount of $353,440., or 70.6% of applications reviewed. Represents 29 projects.
C. Number of applications not approved: 20, in amount of $144,684., or 29.4% of applications reviewed.

III. RESEARCH OBJECTIVES.

A. Immediate Aims and Estimate of Financial Needs for the Period July 1, 1949, to July 1, 1950.

Much has yet to be done in the discovery of new, more effective, less toxic antibiotics to be used against pathogenic agents. Relatively little has been accomplished in the isolation of anti-fungal, anti-rickettsial, and anti-viral agents. Simple accurate methods are needed for evaluation of antibiotic levels in blood and tissues. The difficult problems involved in the purification of new antibiotics must be solved. Purification is important not only for finding the mode of action of a substance but is absolutely essential before any sort of intelligent pharmacological study of the substances can be made. If the pharmacology of an impure mixture is studied the whole research must ultimately be repeated when the pure substance is available.

Unfortunately, all of the preliminary pharmacological work done with penicillin was carried out on impure preparations of totally unknown composition, and most of this has not been repeated as yet on pure preparations. Investigations designed to reveal synergistic relationships between antibiotic substances and other chemotherapeutic agents employed in conjunction with them are also desirable.

It is estimated that for such investigations as have been envisioned for the year July 1, 1949, to July 1, 1950, approximately $500,000 will be needed as follows:

1. Isolation and evaluation of new antibiotics effective against bacterial agents $150,000

2. Isolation and evaluation of antibiotics effective against fungi, viruses, and rickettsiae $100,000

3. Investigation of mode of action of antibiotics $100,000

4. Development of chemical methods for assaying antibiotics $50,000

5. Investigation of synergism $50,000

B. Long-Range Objectives and Estimate of Financial Needs for the Five-Year Period July 1, 1949, to July 1, 1954.

While further clinical studies will undoubtedly be needed on both the older and the newer antibiotics, the major emphasis of the next five years should be directed towards fundamental discoveries and evaluations. The search for new and better antibiotics must be encouraged, and thorough laboratory studies must be a prime requisite preceding intensive clinical application.

The mechanism of action of most of the known antibiotics is still obscure; knowledge of this is essential not only in the elucidation of the mode by which they exert their effects on pathogens, but also for the intelligent, logical construction of more effective and specific chemotherapeutic agents.

A voluminous amount of work remains to be done as regards chemical characterization and, wherever possible, synthesis of antibiotic substances. Only when the latter of these goals is attained will it be possible to achieve an extension of scope comparable to that which developed with the sulfa drugs. Finally, basic studies on both host and parasite metabolism are needed before there can be a full comprehension of the role of antibiotics in infectious processes and host recovery.

On the basis of current investigations and those needed but not yet in progress, and in consideration of the growth of the program as knowledge of it spreads among scientific investigators, it is estimated that for the five years July 1, 1949, to July 1, 1954, $3,000,000 will be necessary adequately to support the needed research in antibiotics. It is anticipated that the allocation of these funds will adhere to the following pattern:

1. (Cf III A.) Similar studies, modified by development $1,250,000

2. Mechanism of action; including pharmacology,

	toxicology, biological chemistry, immunology, pathology, etc.	$1,000,000
3.	Effects on host and parasite metabolism	$150,000
4.	Chemical characterization and syntheses	$150,000
5.	Clinical studies	$450,000

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BACTERIOLOGY STUDY SECTION

June 30, 1948

BACTERIOLOGY STUDY SECTION

I. PROGRESS IN RESEARCH.

A. Overall Progress.

The program of the Bacteriology Study Section has now been underway for almost two full years. During this time, there have been seven meetings of the Study Section at which applications for grants in aid of research have been reviewed. Altogether, the Study Section has approved 61 different projects. Some of these have been activated only since July 1, 1947, and many will not be activated until funds for fiscal year 1949 are available. Including the funds which will be supplied for work in fiscal year 1949, grants totaling more than $700,000 have been recommended for approval by the Study Section to support research in bacteriology. Considering the large size which the Study Section program has already attained and its continuing expansion, a survey of the past activities of the Study Section is appropriate at this time in order that the direction and scope of its future functions be more fully appreciated.

Research projects which began in previous years were continued during fiscal year 1948 on such important bacterial diseases as salmonellosis shigellosis, cholera, tularemia, diphtheria, leprosy, and brucellosis and the chemical behavior of their etiological agents. The effort in some of these projects was directed toward the elaboration of suitable immunizing materials, or of improving diagnostic methods. In others, the emphasis was on the search for new drugs or antibiotics useful in therapy. During the year, additional projects were begun in a number of new fields. For example, several studies on mycotic diseases (sporotrichosis, histoplasmosis, and cryptococcosis) were initiated, as were others on the basic phenomena underlying air-borne infection. A number of new studies were activated on the intermediary metabolism of bacteria, especially as this is related to chemotherapy or serotherapy. Projects on the mechanisms underlying allergy and associated immunological phenomena also were begun.

B. Progress in Specific Projects.

In general, the projects which began during fiscal year 1948 have been underway for so short a period that, as anticipated, only preliminary results, if any, could be reported at this time. Certain other projects, however, which have been underway since the beginning of the Study Section activity in 1946, or even before that date under O.S.R.D. sponsorship, are beginning to yield good results. For example, one study on

experimental cholera has shown that the successful immunization of the guinea pig against cholera vibrios requires the presence of the specific "O" antigen in the administered vaccine. "O" antigen from other enteric pathogens or even the "H" antigen from the cholera vibrio itself is not effective for purposes of immunization. It has also been found that the presence of cholera antibody in the bowel of guinea pigs previously immunized with cholera vibrios influences favorably a subsequent experimental infection with these organisms. Preliminary experiments have indicated that lymphocytes play a role in the transport of cholera antibody from tissues to the bowel lumen because no antibody whatever appears in the bowel of guinea pigs immunized against cholera if these animals be irradiated (150 r) just before their peak titer of serum antibody is attained.

A study on immunization against bacillary dysentery has shown that mice can be protected against dysentery bacilli through the daily oral administration of killed vaccine. Protection is acquired in about nine days. The response to the Sonne' bacillus is substantially greater than that to the Flexner strains which account for a larger number of human cases of dysentery. In another study of dysentery bacilli undetoxified polysaccharide of the Shiga bacillus kept for two years in the lyophilized state lost its toxicity, while retaining its original antigenicity.

Another project has led to the discovery in the last year of six new types of salmonella bacilli through study of the antigen patterns of newly isolated strains of these organisms. Attention has also been given, in the same project, to the antigen pattern of coliform bacteria, some of which have entities in common with the salmonellae. To date, 600 cultures of paracolon bacilli have been studied. One serologic type of these bacilli has been found in each of three distinct outbreaks of diarrhoea, thus possibly suggesting that these bacilli have importance as pathogenic organisms.

In an effort to free diphtheria toxoid from impurities which are believed to cause the untoward clinical effects often seen following its use, one investigator has added protamine to the crude product. The bacillary proteins can be precipitated by this procedure, leaving the toxoid in comparative purity. The toxoid can then itself be precipitated by adding more protaimine or by reducing the ionic strength of the solution. It is possible, finally, to prepare stable concentrated solutions of protamine-precipitated toxoid having 200 times the concentration of the active toxoid found in the

original crude preparation. About 95% of Schick-positive children given a single injection of 25 Lf of protamine-precipitated toxoid become Schick-negative, often within two months. The Schick-negativity is believed to last for at least three years.

In one study on brucellosis, it has been shown through liver biopsy of patients that this disease commonly causes hepatitis and occasionally may be responsible for cirrhosis. Guinea pigs are now being studied after experimental infection in the hope of throwing further light on this observation. Various fractions of brucella organisms have been tested in an effort to find an ideal material for skin testing. In general, dermal reactions elicited with material thus far available are of little use in diagnosis, although of good aid in the prognosis of this important disease. Preliminary studies in chick embryos have shown that a combination of streptomycin and sulfadiazine is effective in treating brucella infections in these embryos. Patients with Brucella abortus who have been treated with a combination of these drugs also have shown marked improvement.

A number of important studies on bacterial metabolism are currently underway and are beginning to yield results which in some cases may go far toward explaining the mechanisms underlying the mode of action of chemotherapeutic drugs.

One very important project concerning the mechanism of air sterilization has resulted in new concepts of the general problem as relating to aerial disinfection by glycols and other chemical agents. An automatic dewpoint meter has been developed during the course of the work for the determination of condensable vapors in air.

It is evident from the forgoing that definite progress is being made under the Study Section program. As the work proceeds and as the scope of activity of the Study Section broadens, there is every reason to anticipate that the contributions which the program makes to knowledge of medicine and microorganisms will multiply.

II. RESUME' OF STUDY SECTION REVIEW OF APPLICATIONS FOR RESEARCH GRANTS (January 1, 1946, to July 1, 1948).

A. Number of applications considered: 133, in amount of $1,139,012.
B. Number of applications approved: 105, in amount of $867,231, or 79% of applications reviewed. (Represents 58 projects)
C. Number of applications not approved: 28, in amount of $219,968, or 18% of applications reviewed.

III. RESEARCH OBJECTIVES.

A. Immediate Aims and Estimate of Financial Needs for the Period July 1, 1949, to July 1, 1950.

The following six major areas or subdivisions of bacteriology deserve emphasis in the immediate future:

1. Morphology, taxonomy, and genetics of microorganisms;
2. Bacterial nutrition, especially the intermediary metabolism;
3. Biochemistry and physiology in the pathogenesis of infectious disease;
4. Immunochemistry;
5. Mechanisms involved in resistance of animal species to pathogenic agents; and
6. Effects of inhibitory agents on microorganisms and their metabolism.

In the tentative apportioning of funds for fiscal year 1950 in anticipation of applications assigned to the Study Section for review, $150,000 should be provided to support each of the first four of the above-designated fields, and $75,000 should be provided for each of the remaining two fields. A total fund of $750,000 would, then, be provided to support all the applications which the Bacteriology Study Section may approve, at least in the six fields mentioned above.

B. Long-Range Objectives and Estimate of Financial Needs for the Five-Year Period July 1, 1949 - July 1, 1954.

It is impossible to predict over the next five years what new fields of interest will develop in bacteriology as research goes on. However, for the most part, any new fields will be extensions or outgrowths of the subject areas listed above as deserving immediate emphasis. Nor is it possible to anticipate for the coming five year period the top level of financial support which should be supplied for research under the Study Section program in any one of or in all the fields of bacteriology. Nevertheless, it would seem reasonable tentatively to suggest continuation in subsequent years of the same level of support proposed for fiscal year 1950 - that is, total support for the five year period in the amount of $3,750,000.

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BIOCHEMISTRY AND NUTRITION STUDY SECTION

BIOCHEMISTRY AND NUTRITION STUDY SECTION

I. PROGRESS IN RESEARCH

A. Overall Progress.

Two extremely important areas in which fundamental research may contribute to medical knowledge and, hence, to human health are the fields of biochemistry and nutrition. It is obvious that biochemical processes are of first importance in the life of any organism and these in turn are demonstrably dependent to a considerable extent on the nutrition of the organism in question. Many valuable additions to our knowledge of biochemistry and nutrition have been contributed by investigators receiving financial support through the U.S.Public Health Service grant-in-aid program. The research projects may be divided into six main groups: (1) nutrition, (2) vitamin studies, (3) enzymology, (4) protein metabolism and chemistry, (5) the biochemistry of disease, (6) the biochemistry of specific substances.

The nutrition studies are being conducted with humans and also with animals. In a majority of the projects with humans few results have been presented due to the preliminary nature of the work and the mass of data to compile and coordinate. These studies include the effect of a deficiency in certain members of the vitamin B complex; pregnancy and the diet; and the food habits and nutritional status of special groups of people.

Vitamin research is still leading to the finding of new vitamins, and several such substances are being isolated by various grantees. Anti-vitamins and other anti-metabolites are being used to produce distinct deficiencies and disorders. This has proved to be an extremely useful tool for the study of biochemical processes.

Enzyme investigations are several in number and are concerned primarily with (1) the fixation of carbon dioxide in the body to form important intermediaries in carbohydrate and fat metabolism; (2) acetylation reactions in the body for the purpose of detoxication, formation of acetyl choline, etc.; (3) mechanism of action of proteinases <u>within</u> the cell; (4) the relationship of vitamins to enzymes. In several of these, as well as in other experiments, good use is being made of radioactive compounds.

Fundamental work on proteins and amino acids is under way. Various bacteria and the protozoan, Tetrahymena, are invaluable tools in these projects. Further studies on the composition and metabolism of proteins, and on the formation of plasma proteins are in progress.

Work on the biochemistry of disease includes the development of simple diagnostic tests for such diseases as pellagra, scurvy, tooth decay, cancer, and hormonal imbalances.

In addition to all of the above subjects, mention should be made of data being collected on such various subjects as the development of new chemical and biological methods for the isolation and the determination of biologically important compounds; fatty acid metabolism; carbohydrate metabolism of the brain; the nature and cause of tooth decay; etc.

B. Progress in Specific Projects.

The relationship of diet to health is being studied intensively by scientists supported by grants from the U.S.Public Health Service. Several different approaches and ingenious techniques are being used. The extremely important problem of the relationship of the nutritional state of the pregnant woman to the course of pregnancy and the health of the infant is being investigated. Elsewhere, the nutritional status of sixty students is being observed over a period of two years. A similar, but more intensive study has been completed on the natives of Alaska with particular emphasis on the effect of diet on the eye ulcers said to be prevalent among Eskimos. Thus far, the most consistent disease associated with a faulty diet in this population group has been found to be tooth decay. Contrary to other reports, only slight irritation of the eye was found. Dietary data have been thoroughly recorded.

Another approach which is yielding excellent results is a study on humans using the combined facilities of a nutrition clinic, a metabolism ward, and a biochemistry laboratory. This group has shown that the extremely high incidence of pellagra in regions where corn is the chief source of protein is due, very likely, not only to a deficiency in niacin, but also to a lack of the amino acid, tryptophane. At the clinic, dietary instruction and treatment are provided to patients and their families. In addition, medical students and nurses receive training in nutrition at the clinic. Other workers have found that vitamin B_6 also seems to be important in pellagra. These investigators have further shown that hospitalized patients, in general, appear to be deficient in all or most members of the vitamin B complex.

Nutrition studies with animals and with microorganisms are also being actively pursued. A protein deficiency did not increase the susceptibility of rats to tuberculosis. Another experiment suggests that folic acid reduces the incidence of hydrocephalus in infant rats. The non-specificity of vitamin E in muscular dystrophy was confirmed. One grantee is engaged in the isolation and chemical identification of an unknown bacterial growth factor. Another grantee has found that a derivative of the vitamin, pantothenic acid, is toxic to many microorganisms. He further discovered that the same anti-vitamin killed mice under certain conditions. One of the goals of this research is the discovery of substances which are toxic to disease-producing bacteria and are relatively non-toxic to man, and hence can be used for the treatment of such diseases.

Studies on enzymes are adding to our knowledge of the fundamental nature of the cell, and in addition can be measured in more immediate terms. A new theory on the action of proteolytic enzymes on ester groups, as well as on the peptide linkage, is being formulated. The formation of fat, hemoglobin and cholesterol has been followed using radioactive carbon. Experiments on the relation of vitamins to enzymes have confirmed the observation that pantothenic acid is required for acetylation processes. They have also shown that biotin is vital in carbon dioxide fixation. In addition, a new enzyme essential in the fixation of carbon dioxide has been isolated and purified. A second enzyme which catalyzes the manufacture of the essential amino acid, methionine, has been discovered recently.

The biochemistry of disease is under attack in many laboratories. A comparison of the chemical constitution of normal lymph tissue and pathological tissue from cases of Hodgkin's disease, leukemia and lymphosarcoma is being made to determine the changes produced by the various diseases. The use of serum precipitable iodine as a diagnostic aid in thyroid, pituitary, and also pregnancy dysfunctions is being analyzed. Harmful side effects following the intravenous infusion of amino acids and their metabolic fate are under investigation. Experimental edema is now being used for the study of edema of the brain and other tissues. An attempt is being made to cure liver damage caused by exposure to certain commercial compounds such as carbon tetrachloride and chloroform. The function of the liver in the formation of plasma proteins is being ascertained.

Additional projects on proteins include a detailed investigation of the proteins of cell nuclei. Nucleic acid fractions are being synthesized. The nature of the proteins of certain unusual heat-resistant thermophilic organisms is the subject

of another interesting problem. Another group is working on complex proteins such as are found in the immunologically important antigen-antibody reactions and also in the normal constituents of cells such as nucleoproteins. Another laboratory has discovered a new phosphorus-containing compound in heart muscle.

II. RESUME OF STUDY SECTION REVIEW OF APPLICATIONS FOR RESEARCH GRANTS (January 1, 1946, to July 1, 1948):

A. Number of applications considered: 182, in amount of $1,479,405.
B. Number of applications approved: 126, in amount of $861,057., or $69.2% of applications reviewed. (represents 72 projects).
C. Number of applications disapproved: 56, in amount of $534,296., or 30.8% of applications reviewed.

III. RESEARCH OBJECTIVES.

A. Immediate Aims and Estimate of Financial Needs for the Period July 1, 1949 to July 1, 1950.

On the basis of the yearly growth of research in biochemistry and nutrition supported by the U.S. Public Health Service since 1946, it has been estimated from a curve that the financial needs for FY 1950 in this field are approximately $800,000. In terms of the research actually sorely needed to improve the health of the nation, the figure should be considerably higher than this amount; however, the sum quoted is closer to the actual support which will be requested.

The $800,000 should be apportioned to support the following immediate research objectives:

Nutrition	$180,000
Biochemical Studies on Proteins, Fats and Carbohydrates	130,000
Vitamin Studies	130,000
Enzyme Studies	100,000
Study of Cell Regulators (hormones, etc.)	90,000
Biochemistry of Specific Substances	90,000
Methodology	80,000
	$800,000

B. Long-Range Objectives and Estimate of Financial Needs for the Five-Year Period July 1, 1949 to July 1, 1954.

With the same curve as that used under III A, the financial needs for the indicated five-year period can be summarized as follows:

FY 1950	$800,000
FY 1951	950,000
FY 1952	1,000,000
FY 1953	1,000,000
FY 1954	1,100,000
Total.....	$4,850,000

The long-range research objectives should include the items listed under III A, with perhaps a somewhat greater emphasis on problems dealing with the fundamental reactions and structure of the normal cell. Consequently, more money should be spent in support of research on enzymes; on the chemical constitution of normal and abnormal cells; and on the development of specific powerful tools for probing into the mysteries of the cell; these would include antimetabolites and radioactive substances. Only by active support of fundamental research along these lines can the demands of medicine for basic information be adequately met.

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CARDIOVASCULAR STUDY SECTION

June 30, 1948

CARDIOVASCULAR STUDY SECTION

I. PROGRESS IN RESEARCH.

The Cardiovascular Study Section has now completed two years' service recommending research projects in its field to the National Advisory Health Council. On May 15, 1947, the Chairman addressed to the Director of the National Institute of Health a summary of the consensus of the Study Section with regard to particular opportunities and needs in cardiovascular research. The opinions expressed in that communication which were based upon the experience of the Study Section members as investigators, teachers, and practitioners in the field, are in the process of being supplemented by an authoritative survey comprehending all institutions concerned with cardiovascular disease in this country. The director of this survey is Dr. Hiram E. Essex, himself a distinguished contributor to cardiovascular research, whose services as special consultant to the Cardiovascular Study Section have been made available through the courtesy of the Mayo Foundation. It is anticipated that a report of this survey will be in hand early in 1949.

The knowledge to be gained by such a survey should inevitably assist greatly in identifying the neglected areas in which research is wanting and in stimulating more definite interest in certain institutions in this branch of investigation. It is to be confidently anticipated that the survey will, incidentally, confirm the present well-founded impression that additional manpower, brain-power, and physical facilities are currently outstanding needs.

The applications which have been reviewed by the Study Section and the projects which have been recommended tend to group themselves in certain patterns. These patterns reflect the scientific preoccupation of the investigators. The preponderant interest in hypertension, arteriosclerosis, and cardiac failure is consistent with the importance of these conditions to national health.

High blood pressure and arteriosclerosis are companion plagues. Affecting many persons in the fifth decade of life and beyond, these diseases are responsible for a large majority of deaths from cardiovascular causes. Hypertension, we know, develops with some forms of kidney disease but, in the greater proportion of instances, it arises obscurely and progresses insiduously, often to a miserable termination. It provokes irreversible thickening and narrowing of small arteries. It often places an intolerable burden upon the heart provoking failure of the

heart muscle. Finally it is arteriosclerosis, often abetted by hypertension, which is at the basis of coronary thrombosis, the usual cause of fatal "heart attacks."

It is a particular challenge of these conditions that they frequently afflict their victims in the prime of active life. With a larger proportion of the population reaching advanced age the importance of this problem will signigicantly increase.

HYPERTENSION

It is possible to report progress under these projects toward the understanding of the true nature of hypertension and toward the detection of agents in the blood which may be responsible for the rise of blood pressure. Extracts of blood of hypertensive patients have been shown to contain unidentified substances which upon injection into rats, consistently raise the blood pressure of those animals. Another group of investigators has isolated, purfied, and partially identified, a substance evidently responsible for the constricting effect of normal human serum; this is called serotonin and may be elaborated at the site of clots in blood vessels.

The effects upon blood pressure of various chemicals, some elaborated in the body (hormones), and others prepared by chemical synthesis are being thoroughly examined. It has been shown that hypertensive patients acquire a further and, frequently a sustained, elevation of blood pressure upon the administration of one of the products of activity of the adrenal cortex (desoxycorticosterone acetate). Preliminary results suggest that other, antagonistic, substances are also elaborated in the adrenal cortex, which decrease blood pressure.

Considerable interest is currently being displayed in chemical compounds which specifically interfere with the constrictor activity of the nerves supplying small arteries. It is possible to distinguish differences by this means between hypertensive and normal persons and among various groups of patients with hypertension. It is not yet feasible to employ these substances in therapy.

The surgical treatment of hypertension by section of the nerve supply of blood vessels is being critically evaluated by the careful study of patients before operation and for long periods thereafter. A definitive answer is not likely to be found without years of study.

The role of the kidney in the production of high blood pressure is being investigated, as are also the effects of hypertensive disease upon the kidney. In the late, "malignant," stages of hypertensive disease rapid and progressive kidney failure is a familiar complication. It has been demonstrated that the onset of this stage of the disease is frequently heralded by characteristic changes in certain protein (globulin) constituents of the blood.

The dramatic relief obtained in some cases of hypertension by the use of diets which presumably reduce the kidneys' burden by severely limiting the intake of salt and protein have stimulated study of the physiological effects of the rice diet of Kempner and other types of dietary treatment. It is to be hoped that the fundamental value of such therapy, as well as the reasons for the occasional failure, will be elucidated thereby.

ARTERIOSCLEROSIS

It has been commonly, and incorrectly, assumed that "hardening of the arteries" is an inevitable part of the natural process of aging. However, a more fruitful concept is now spreading among investigators: that arteriosclerosis is a disease in itself.

Examination of arteries from patients with arteriosclerosis has shown that the early lesions in the arterial wall contain deposits of lipid (fatty) material. The further identification of forms of cholesterol as principal constituents of these plaques in the vessel's lining has quite logically focused attention upon these substances, their absorption, distribution, and fate in the body. It has been demonstrated, for example, that the amount of cholesterol in the blood of arteriosclerotic subjects is not uniformly greater than that in the blood of normal persons, but is characteristically subject to wide variations.

Progress toward the understanding of this basic degenerative process has been hampered heretofore by the lack of a comparable disease in animals. Arteriosclerosis could be provoked only in certain species, notably chickens or rabbits, and then only after long, laborious, experiments under unnatural conditions. Within the last two years under one of these projects important advances have been made in this direction. It has been demonstrated that arteriosclerosis will develop in dogs fed cholesterol if at the same time the activity of the thyroid gland is depressed by the administration of suitable chemicals. The investigators have also been successful in producing arteriosclerosis rapidly and uniformly in animals by the administration of certain forms and derivatives of cholesterol similar to those present in the arteriosclerotic vessel walls. These had not previously been employed in such experiments.

The implications of the success of these observations are important and obvious. They place in the hands of investigators experimental objects which should provide clear opportunity for better understanding of the fundamental processes involved in arteriosclerosis.

In one project three hundred men between the ages of 45 and 55, including the governor of the state, have been carefully examined and tested. They have undertaken to cooperate in undergoing similar examinations and tests over a period of years.

This will constitute a large scale "natural experiment." If, as may be expected, some members of this group develop cardiovascular disease, some important steps in the natural history of this process will have been described through these observations.

PHYSIOLOGY OF THE CIRCULATION

Investigations are being extended under other projects to the study of the circulation in man and animals in normal and diseased states. There have emerged better understanding of several aspects of the circulation, as well as penetrating analysis of the fundamentals of electrocardiography.

Attention is also being devoted to the development and evaluation of still newer methods for the study of the heart and measurement of the circulation. These, it is to be anticipated, will widen the scope of inquiry and be fruitful of new knowledge in the domain of cardiac physiology and disease.

HEART FAILURE

The basic methods for treating the heart in failure have changed but little in 150 years. The state of "dropsy," which is a frequent accompaniment, has been benefitted by stimulating the flow of urine with various diuretic drugs or chemicals. In recent years interest has revived and broadened concerning effects of changes in the circulation, particularly circulatory failure, on kidney function. New methods permit more accurate study in patients. In several projects these are being applied to the study of the natural history of heart failure, its effects upon the kidney, and its relief by improving certain kidney functions.

Unfortunately these observations are complicated and tedious; this limits the number which can be made, and restricts their frequent repetition. However, steady progress and some new knowledge can be reported. The circulation to the kidney has been shown to diminish considerably with exercise in normal man, and falls even more in some patients with heart failure. In certain types of circulatory failure deficient blood flow through the kidney and diminished output of salt seem to be related. The significant fact has emerged from such investigations that cardiac dropsy is not a single entity; the same condition may develop in several ways. As these findings can be elaborated and further analysed it is not too much to hope that treatment can be more helpfully fitted to the individual patient.

ANTICOAGULANT THERAPY IN CASES OF CORONARY THROMBOSIS

Just prior to the beginning of the war two types of substances became available which have the property of suppressing the tendency of the blood to clot. Heparin, from ox liver, and dicumarol, from sweet clover, were prepared in adequate purity for administration to patients, the former by injection and the latter by mouth.

For many years it has been recognized that most serious and often fatal complications of coronary thrombosis result from the formation of clots against the injured wall of the heart which then break off and, carried in the blood stream, cause injury in the brain or in other organs.

In the spring of 1946 discussions took place between representatives of the American Heart Association and the Cardiovascular Study Section which resulted in the organization and support of a cooperative investigation on the effects of anticoagulants upon the death rate and the incidence of complications in coronary thrombosis. One thousand cases were collected and critically studied in 19 institutions in all parts of this country. By the spring of 1948 it was evident that by the early and controlled administration of substances which suppress the clotting power of the blood the death rate from coronary thrombosis and incidence of the most serious complications can be substantially reduced. This knowledge having been reported, protection of these patients by anticoagulant therapy has already become a widespread practice.

Particular attention is drawn to this project as a collaborative enterprise conducted in many institutions and made possible by public funds. The investment has already been well rewarded.

II. RESUME OF STUDY SECTION REVIEW OF APPLICATIONS FOR RESEARCH GRANTS (January 1, 1946, to July 1, 1948).

A. Number of applications considered: 149, in amount of $2,415,457
B. Number of applications approved: 104, in amount of $1,369,465, or 70% of applications reviewed. (represents 56 projects).
C. Number of applications disapproved: 45, in amount of $783,574., or 30% of applications reviewed.

III. RESEARCH OBJECTIVES

A. Immediate Aims and Estimate of Financial Needs for the Period July 1, 1949, to July 1, 1950.

The immediate aims for the fiscal year 1950 are to continue the Cardiovascular studies already in operation. It is estimated that approximately $1,000,000 will be required for this purpose.

Hypertension	$400,000
Arteriosclerosis	300,000
Coronary Thrombosis	150,000
Other	150,000
	$1,000,000

The estimates given here represent only the funds which will be needed by the Cardiovascular Study Section and should not be interpreted as reflecting overall needs in the field. Many studies of great importance to the Cardiovascular program should logically be carried in the Physiology, Metabolism and Endocrinology, Pharmacology and other Study Sections. In addition, the estimates apply only to scientific research and so do not include many aspects essential in an overall program of heart disease control, such as postgraduate physician training in diagnosis, therapy, fellowship programs for training, control and education activities.

Likewise these funds will continue to be directed primarily toward supporting research on subjects and in fields not already adequately covered by other granting agencies or other sources of financial support.

B. Long-Range Objectives and Estimate of Financial Needs for the Five-Year Period July 1, 1949 - July 1, 1954.

With regard to the most fruitful directions in which additional funds can be extended to research on heart disease, the Study Section has certain suggestions to offer. In the first place there are certain fields in which expended funds would most certainly produce tangible results within predictable time. Here one must consider the forms of cardiovascular disease which are to greater or lesser degree reversible. This category will include first such conditions as bacterial endocarditis of which there are several thousand cases in this country yearly. The large majority of these can be cured by appropriate chemotherapy. The proportion can probably be considerably enlarged by early diagnosis and intelligent prophylaxis. There is need for further investigation regarding the choice of antibiotics and the most effective dosage.

There is a second group of cardiovascular conditions which are, to an important extent, susceptible to treatment by surgery. This includes first various types of diseases of the blood vessels, vasospastic, or sclerotic. Attention should be directed to improving treatment, to facilitating early diagnosis, and to the evaluating, by objective means, results of different forms of therapy.

The results obtained during the last few years in the surgical treatment of various congenital abnormalities of the heart and aorta invite the hope that by careful study and experiments on animals the physiological barriers which now oppose extension of surgery on the heart may be overcome. Attention is called to the work going on under research grant project, RG-517, which is directed to the development of a device to replace the heart and lungs of uman patients for brief periods. Such an apparatus, if successful, would permit surgical procedures on the heart which cannot now be contemplated.

While dramatic results may be anticipated in the categories just mentioned, it is only fair to emphasize that a relatively small proportion of persons who would otherwise die of heart disease will be affected. The great scourges in this field are more common.

The need cannot be over-emphasized for continuing clinical and experimental study of rheumatic heart disease. Chiefly affecting young people this is a principal cause of death in the third decade of life. The recent promise of certain types of animal experimentation leads one to expect that concentrated study may make it possible to produce "rheumatic fever" in animals and to investigate the control and treatment of the disease under laboratory conditions. Along with this clinical investigation should be conducted. A most fruitful type of research, if successful, would be that directed to the development of means of specific immunization against streptococcal infection which so frequently precedes the onset of rheumatic fever.

Syphilitic cardiovascular disease can be usefully studied. Its control will certainly depend fundamentally upon the improvement in the treatment of syphilis, especially in its early stages.

Hypertension is already being widely investigated. The present obvious needs are for more information regarding the role of the kidney and of the nervous system in the development and maintenance of high blood pressure.

In view of the relief sometimes afforded by operative interference with the sympathetic nerve supply, attack should be fostered to accomplish this interruption by chemical means with sympatholitic substances. There is perhaps an opportunity here for a multi-institutional project directed at this target.

Finally there is the large and little understood category of arteriosclerosis. There is already in progress a study of two contrasting groups of supposedly normal persons: one group in their twenties and another in their forties. Such long term studies should disclose, amoung other data, the differences which characterize persons liable prematurely to develop arteriosclerosis. These differences may turn out to be constitutional, biochemical, or even psychiatric. This type of investigation, though tremendously tedious, is essential to an adequate understanding of the natural history of this disease. Experimental and clinical investigation may be pushed and will probably be most fruitfully devoted to the field of biochemistry and particularly of metabolism.

It is extimated that by fiscal 1955 these activities should reach a level of about $5,000,000 per annum, i.e., $15,000,000 would be necessary for these 5 years, as follows:

1950	$1,000,000
1951	$2,000,000
1952	$3,000,000
1953	$4,000,000
1954	$5,000,000

These estimates are admittedly based on incomplete information since complete information does not exist. However, the Cardiovascular Study Section is now making a National Survey of Heart Disease Research, the data from which can be used to form accurate, factual estimates of future needs. This information is expected to be complete January 1, 1949.

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DENTAL STUDY SECTION

DENTAL STUDY SECTION

I. PROGRESS IN RESEARCH.

A. Overall Progress.

The dental projects supported by the U. S. Public Health Service can be grouped into four main fields of research: (1) nutrition; (2) oral inflammatory changes; (3) effect of fluorides; (4) oral bacteriology.

The nutrition experiments are being conducted chiefly with rats. They deal largely with producing dietary deficiencies in substances known to be important in the development and maintenance of sound teeth and bones and also healthy oral structures. These deficiencies would include lack of protein, calcium, phosphorus, vitamins C and D and certain members of the vitamin B complex.

Research on oral inflammatory changes is advancing with great rapidity. Good results have been obtained in studies on gingivitis, the healing of dental pulp tissue, and the cause of such chronic diseases of the mouth as ulcers of the mucous membrane.

The results accruing from the extremely important work with fluorides leads to the belief that wide-spread clinical application will be forthcoming in the near future. Continued support of this type of research is almost certain to result in a drastic reduction in the appallingly high percentage of cases of human dental caries.

Other vital fields of investigation include bacteriology, biochemistry, physics, genetics, and related subjects. The studies in bacteriology and genetics are of particular interest. Great forward strides have been made in establishing a causal relationship between oral bacteria and such oral diseases as ulcers of the mucous membrane. It has been possible to demonstrate with rats the great importance of inheritance on the susceptibility of tooth decay.

B. Progress in Specific Projects.

The relationship of diet to oral health is being studied by several scientists supported by grants from the U. S. Public Health Service. The extremely important problem of the effect of maternal nutrition on bones and teeth is being investigated with rats. It has been found that the long bones of offspring from females on a diet deficient in riboflavin were somewhat

shorter than those of the normal controls. Another experiment on the influence of (a) riboflavin and (b) vitamin B_6 deficiency on the bone and tooth development of mice is in progress. There was a marked decrease in the rate of growth and ossification in the jaw bones of riboflavin deficient mice. In vitamin B_6 deficient animals growth of cartilage and formation of bone ceased after a few weeks. There also were inflammatory and degenerative changes in the mouth and poor growth of tooth dentine.

Another dietary study, relating a deficiency in protein to the growth and development of oral structures in the rat, shows thus far that the bony framework of the experimental animals was soft whereas that of the controls appeared firm and massive. However, the teeth were anchored firmly in their alveolae. Preliminary results from another group show no effect of a moderate restriction of calcium or phosphorus in the production of dental caries.

Important advances in the field of oral inflammatory changes have resulted from the research of grantees. A vital new finding is that, contrary to former belief, the delicate pulp tissue of teeth can be healed when exposed accidentally or during drilling. This should decrease suffering and loss of teeth considerably. A method for measuring more accurately, inflammation of the gums has been worked out, allowing for a careful study of gingivitis, a very wide-spread disease. An intensive program on the health of the gingivae in pregnancy, diabetes and certain diseases of the blood is in progress. To date, it has been shown that the gingivitis of pregnancy is not specific for pregnancy. A comprehensive survey to find the underlying causes of such chronic diseases of the oral mucous membrane as ulcers is being made. Blood tests on seventy-five patients have shown elevated values for cholesterol, red cell sedimentation rate and globulin in 20-30% of the cases. In addition, reduced amounts of vitamin C were observed in 33% of the patients. These investigators also found that a deficiency of certain vitamins (pantothenic acid or a combination of biotin and folic acid) result in lesions of the tongue of rats. A careful study of the bacteria responsible for mixed infections of the oral mucous membrane has resulted to date in the successful production, after subcutaneous injection, of abscesses in guinea pigs. Thus, these results suggest strongly that these microorganisms play an important role in the production of oral ulcers.

Since the extremely important discovery that fluorides markedly reduce tooth decay, careful research is continuing along these lines. It has been found recently that various substances, fluorides and others, actually increase the hardness of enamel

and likewise tend to protect the teeth against decay. Tin fluoride proved to be the most effective compound tested thus far. Maximum hardness was obtained after twenty-five minutes of treatment which consisted merely of swabbing the material on the teeth. This protective action of tin fluoride was also shown in test tube experiments with teeth and acetic acid.

One of the most important investigations is a long-range study of the relationship of heredity to susceptibility to tooth decay in rats. This fundamental research has been in progress for over ten years through at least eighteen generations of rats. The date of appearance, location, and approximate size of every cavity in the lower molars has been recorded. Heredity has been found to be an extremely important factor in tooth decay, so much so, that these workers have produced, through proper cross-breeding, a strain of rats which is very resistant to dental caries. In addition, a strain has been bred which is very susceptible to tooth decay. The implications of these results with relation to dental caries in humans are both profound and obvious.

In certain other long-range projects few results have been presented due to the preliminary nature of the work and the mass of data to compile and coordinate. In one such study the growth of the human head from the third month to the eighth year of life is under investigation. Early results from another extremely important series of experiments on bone growth and healing in dogs have shown that it appears possible to cause the laying down of bone salts across a gap an inch long in bony structures. This is being done with a hardened mixture of gelatine and the chemical salts present in bone, cut and shaped to be inserted into the space experimentally removed from the leg bone.

An interesting approach to the determination of some of the causes of pain produced by drilling is the study of the vibration of dental handpieces. To date an oscillograph and a wide range variable frequency generator have been set up to pick up the complex motions of the handpiece, to translate them into varying electrical currents, and to study them on an oscillograph screen. With this set-up data will be collected on the nature of these vibrations of the dental handpiece and on the damage to tooth structures resulting from such vibrations.

II. RESUME OF STUDY SECTION REVIEW OF APPLICATIONS FOR RESEARCH GRANTS (January 1, 1946, to July 1, 1948).

A. Number of applications considered: 80, in amount of $493,515.
B. Number of applications approved: 66, in amount of $295,372., or 82.5% of applications reviewed. (36 projects).
C. Number of applications disapproved: 14, in amount of $172,979., or 17.5% of applications reviewed.

III. RESEARCH OBJECTIVES.

A. Immediate Aims and Estimate of Financial Needs for the Period July 1, 1949, to July 1, 1950.

On the basis of the yearly growth of dental research supported by the U. S. Public Health Service since 1946, it has been estimated from a curve that the financial needs for FY 1950 in this field are approximately $500,000. In terms of the research actually sorely needed to improve the health of the nation, the figure should be considerably higher than this amount; however, the sum quoted is closer to the actual support which will be requested.

The $500,000 should be apportioned to support the following immediate research objectives:

Physical-Chemical Studies	$130,000
Oral Tumors and Inflammatory Changes	60,000
Epidemiology of Common Dental Diseases	120,000
Experimental Biology in Relation to Dental Problems	80,000
Biostatistics	15,000
Oral Bacteriological and Chemical Studies	25,000
Oral Therapy	20,000
Miscellaneous	50,000
	$500,000

B. Long-Range Objectives and Estimate of Financial Needs for the Five-Year Period July 1, 1949 to July 1, 1954.

With the same curve as that used under III. A, the financial needs for the indicated five-year period can be summarized as follows:

FY 1950	$500,000
1951	700,000
1952	900,000
1953	1,000,000
1954	1,100,000
Total	$4,200,000

The long range research objectives should include the items listed under III. A, with perhaps a somewhat greater emphasis on such fundamental problems as the development and maintenance of sound teeth and healthy supporting structures. Consequently, more money should be spent in support of research on enzymatic processes controlling the growth of teeth and gums; on the chemical constitution of normal and carious teeth; and on the development of specific powerful tools for probing into the mysteries of the cell; these would include radioactive substances. Only by thus going directly to the fountainhead of information can scientists solve the ultimate riddle of life and health.

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GERONTOLOGY STUDY SECTION

GERONTOLOGY STUDY SECTION

I. PROGRESS IN RESEARCH

Until recently the problem of increasing life span has remained a largely neglected field of interest. Now, however, with greater specialization in every branch of medicine and with an increased focusing of attention upon the basic problems of senescence, there is every hope that this important subject will receive the attention it merits. Funds made available through the Research Grants Division have been of especial help in giving impètus to investigations which may ultimately yeild valuable knowledge in the field of endeavor.

A number of projects are now in operation under the support of Research Grants funds in which worthwhile progress is being made. As an example, the influence of continued exposure to stress on degenerative changes in tissue is being investigated and there is reason to believe that such studies may yield important information concerning all gerontological problems. It has been shown by a number of investigators that under certain conditions underfeeding may prolong life and therefore the problem of caloric intake as related to aging processes is also being investigated.

Another important approach to the study of the problem of aging is the determination of the rate of excretion of steroid hormones at various ages. It has been shown that the pattern of steroid excretion changes markedly in aged men and further studies are being pursued in this direction.

II. RESUME OF STUDY SECTION REVIEW OF APPLICATIONS FOR RESEARCH GRANTS (January 1, 1946, to July 1, 1948.)

A. Number of applications considered: 43, in amount of $913,601.
B. Number of applications approved: 31, in amount of $479,360., or 72% of applications reviewed. (Represents 15 projects.)
C. Number of applications disapproved:12, in amount of $354,704., or 28% of applications reviewed.

III. RESEARCH OBJECTIVES.

A. Immediate Aims and Estimate of Financial Needs for the Period July 1, 1949, to July 1, 1950.

The immediate aims of the Gerontology program are to continue studies already in progress and to initiate certain others which may be of immediate significance. Among these are the following:

1. Effect of diet on longevity and the development of degenerative diseases.

2. Age changes in endocrine function - such as steroid excretion, thyroid function, adrenal cortex.

3. Changes in cellular calcium metabolism with age.
4. Changes in carbohydrate metabolism with age.
5. Age changes in renal function.
6. Effect of age on physiological responses to stress.
7. Fat deposition in arteriosclerosis.
8. Effect of age on enzyme systems of specific organs and tissues.

It is extimated that approximately $700,000 will be needed for this purpose during the fiscal period July 1, 1949 to June 30, 1950.

B. Long-Range Objectives and Estimate of Financial Needs for the Five-Year Period July 1, 1949 - July 1, 1954.

The long range objectives are studies of the entire process of aging in all its ramifications. Such studies would be made along the following general lines:

1. Changes in metabolism with age.
2. Changes in physiological response to stress with age.
3. Psychological changes with age.
4. Changes in work capacity with age.
5. Metabolic and biochemical aspects of arteriosclerosis.

It is estimated that the financial needs to carry out these studies for the period July 1, 1949 to July 1, 1954 will be approximately $3,500,000. Laboratory buildings are urgently needed and any construction of such buildings may add a number of million dollars to the financial needs.

A more comprehensive phase of the problem is shown by the accompanying outline:

GERONTOLOGY PROBLEMS	SUGGESTED RESEARCH
A. BASIC PROCESS OF SENESCENCE which results in loss of ability and in progressively increasing death rate with advancing age.	
1. Increased Death Rate with Advancing Age.	a. Subject healthy animals of different ages to known causes of death, and determine resistance in relation to hormone therapy, or to other experimentally controlled conditions.

b. Study of the nature of the moribund state in humans, or in animals, at various ages - by means of chemical and physiological tests.

c. Statistical studies on the extent that the increasing death rate may result from the accumulation of pathological conditions, rather than from basic senescent changes.

d. Determination of ability to form antibodies at different ages.

2. Loss of Physical and Mental Abilities with Advancing Age. — Physical and psychological studies of adults of different ages.

B. CHANGES IN COMPOSITION AND STRUCTURE with advancing age.

1. Changes in Chemical Composition of fluids, cells and tissues. — Further chemical analyses on inorganic and organic constituents of the cell and of the intracellular fluids.

2. Histological and Anatomical changes in the tissues and organs. — Further histological and anatomical studies of cellular changes and of the accumulation of collagen or other materials.

C. FUNCTIONAL CHANGES in metabolism or physiological activity, with advancing age.

1. Alterations in Chemical Functions of the cells and tissues.

I. Hormones: especially the anterior pituitary, the pituitary, the thyroid, and the adrenal hormones.

a. Study of hormone production, activities, and effects at different ages, with quantitative determinations of steroid hormones.

	b. Development of quantitative methods for other hormones.
II. Enzymes	Study of enzyme production and activity at different ages.
III. Fats and Cholesterol	a. Study of fat and cholesterol metabolism at different ages with reference to deposition in atherosclerosis (including tagged atom studies.)
	b. Study of nutritional utilization versus toxicity of fats.
IV. Collagen	a. Study of collagen deposition in sclerotic plaques.
	b. Study of collagen formation and deposition in tissues at different ages.
V. Vitamins	Study of vitamin metabolism and requirements at different ages.
VI. Proteins, amino acids and other constituents of the diet.	a. Determination of optimum requirements of various dietary constituents relative to life span.
	b. Determination of changes in dietary requirements with advancing age.
	c. Metabolic studies making use of tagged atoms.

2. Cell and Tissue alterations.

I. Changes in cells which result in altered function and physiology	Continued study of resistance of cells in older tissues to toxic agents.
II. Cell Pathology (neoplastic growth and degenerative changes.)	Studies of relation of age to effects of carcinogenic substances.

3. Changes in Organ Physiology

I. Vital Function Changes	a. Study of cardiac output at various ages.
	b. Study of recovery from shock at various ages.
	c. Study of effects of stress at various ages.

	d. Study of renal function at various ages.
	e. Study of vital capacity at various ages.
	f. Study of gastric activity at various ages.
II. Changes in the Circulatory System.	a. Study of Capillary permeability.
	b. Study of blood volume changes.
	c. Study of arterial elasticity changes.
	d. Study of shock mechanism.
	e. Other studies on the physiology of the circulation.
III. Changes in the Digestive Tract.	
IV. Changes in the Reticulo-endothelial System.	
V. Changes in the Sense Organs.	Studies of changes in the eyes and ears.
VI. Changes in the Skin	
VII. Changes in the Reproductive System.	
4. Mental Changes	Psychological studies at different age levels.
D. DISEASES OF ADULTS--ETIOLOGY AND PATHOLOGY	
1. Arteriosclerosis	a. Continued studies of the role of cholesterol.
	b. Study of the role of neutral fat and the relationship of the fat depositing mechanism.

c. Study of mechanism of collagen deposition.

d. Study of predisposing conditions.

2. Coronary occlusion.

3. Rheumatic heart disease.

4. Other heart diseases.

5. Cerebral hemorrhage.

6. Hypertension.

7. Nephritis.

8. Arthritis and Rheumatism.

9. Cancer.

10. Other adult diseases.

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HEMATOLOGY STUDY SECTION

HEMATOLOGY STUDY SECTION

I. PROGRESS IN RESEARCH.

A. Overall Progress.

During fiscal year 1948, research was initiated in several new subjects and in a number of institutions where it had not previously been attempted. Deliberate stimulation of research in certain fields has been achieved by means of a series of small informal seminars sponsored by the Study Section. In these seminars, the newcomers and established investigators meet around the conference table to discuss ideas, methods, and current needs in the field. Theories are formulated and discussed. Seminars have been held on the subjects of folic acid in anemia, blood coagulation mechanisms in hemorrhagic diseases, and on the formation and destruction of red blood cells. Several excellent research projects have arisen as a direct result of each of these meetings. Recognizing the need for a concerted attack upon the problem of isolating and identifying the natural blood-forming factor in liver, the Study Section has organized and initiated a large cooperative program in this area. The fractionation and clinical testing are well under way, and prospects for an early solution of the problem are very good.

B. Progress in Specific Projects.

In the field of anemia, rapid progress has been made in studies of the new vitamin, folic acid. Clinical and laboratory studies of this substance continue under four different grants. In addition to defining the therapeutic usefulness of folic acid, these laboratories have made major contributions to the basic knowledge of its role in metabolism. An interesting by-product has been the development of folic acid antagonists which give promise of being valuable therapeutic agents in the treatment of acute leukemias which have hitherto been rapidly fatal. Valuable contributions have also been made in the basic physiology of the anemias of infection and the hereditary mechanisms and physiology of Mediterranean anemia, sickle cell anemia, and the sickle cell trait.

Excellent progress is being made in coagulation studies. A strain of dogs with hereditary hemophilia closely resembling that of man has been studied, and the problems of breeding and rearing these dogs appear to be well on their way toward solution, and it is hoped that this strain of dogs will provide suitable animal material for careful studies of hemophilia. Basic chemical and physiological studies

of the substances involved in blood clotting have been very active and several substances have been isolated in relatively pure form. With these substances, more accurate clinical studies of hemorrhagic diseases are being undertaken under several grants with encouraging results.

Clinical and laboratory studies of blood groups are being carried out under five grants and are yielding information of basic importance and of immediate practical value in the field of blood transfusions and blood banks. Significant progress has been made toward complete purification of several of the blood group substances.

The chemical fractionation of plasma proteins has continued under several grants. As the fractions are isolated and identified, they are subjected to physical and chemical studies of molecular structure, and are then released for biological study and clinical application. Of the many fractions under investigation, several are of particular interest in the field of hematology. These include the iron-binding globulin, which is of basic importance in the understanding of certain anemias, the immune globulins, and the various proteins which are concerned in the clotting mechanism.

Grants in the field of white blood cells continue to yield interesting basic information, particularly in connection with studies in immunity. These include studies of the site of antibody formation and of factors involved in phagocytosis. Other productive studies under way deal with Hodgkin's disease, the metabolism of the white cells, and the effect of various nutriments and toxic substances on the formation and destruction of leucocytes.

II. RESUMÉ OF STUDY SECTION ACTIONS ON APPLICATIONS FOR RESEARCH GRANTS (January 1, 1946, to July 1, 1948).

A. Number of applications considered: 117, in amount of $1,412,138.
B. Number of applications approved: 92, in amount of $885,136, or 78.6% of applications reviewed (represents 45 projects).
C. Number of applications disapproved: 25, in amount of $173,276, or 21.4% of applications reviewed.

III. RESEARCH OBJECTIVES.

A. Immediate Aims and Estimate of Financial Needs for the Period July 1, 1949, to July 1, 1950.

A careful analysis of current conditions indicates that a minimum of $800,000 will be required to meet the needs of fiscal year 1950. At the beginning of fiscal year 1949,

the projects approved during fiscal year 1948, plus the continuing projects, will increase the Study Section budget 40% over fiscal year 1948, and it appears that again the funds will be exhausted at the beginning of the fiscal year so that all grants approved during fiscal year 1949, will accumulate as obligations against the 1950 budget. If present trends continue, approximately $640,000 would permit the Study Section to begin fiscal year 1950 without funds for new projects but with sufficient funds to continue support of worth-while current projects and to activate projects approved during fiscal year 1949. The Study Section feels strongly that additional funds should be available in an amount sufficient to permit immediate activation of projects approved during fiscal year 1950 and to initiate forward financing of some of the long-term projects in key laboratories. The increase of funds to a total of $800,000 would permit these objectives to be reached.

B. Long-Range Objectives and Estimate of Financial Needs for the Five-Year Period July 1, 1949 - July 1, 1954.

The field covered by the Hematology Study Section encompasses diseases of the blood and blood-forming tissues in addition to blood transfusions, blood substitutes, and blood fractions. This field has long been an important and active area of research. It assumes even greater significance with the advent of the atomic bomb and the very real possibility of civilian bombing. Diseases of the blood are the major cause of delayed death after an atomic bomb explosion, so that preventive and therapeutic measures for dyscrasias will be major civilian as well as military problems. In any long-term planning, it would therefore appear unwise to reduce financial support of research in this field. The extent to which financial support should be increased is difficult to determine. It is obvious that the program has not yet reached a point where it should be leveled off, but it is entirely possible that this point may be reached during the next five to ten years. The following figures represent minimum financial needs, estimated on the basis of the present trend:

Year	Amount Needed
1950	$ 800,000
1951	960,000
1952	1,909,000
1953	1,190,000
1954	1,300,000
Total	$5,340,000

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MALARIA STUDY SECTION

MALARIA STUDY SECTION

I. PROGRESS IN RESEARCH

A. Overall Progress

When the Office of Scientific Research and Development was discontinued at the end of World War II, it was evident that many of the potential benefits of the malaria program sponsored by that Agency would be lost through failure to complete the experiments necessary to bring the program to a satisfactory conclusion. It was for this reason that the Malaria Study Section was organized. Through their efforts it has been possible to "clean up" many of the unsolved problems left by the wartime program, while at the same time the stage was being set for new advances in basic research.

Whereas the wartime program of malaria research was concerned chiefly with the chemotherapy of malaria, in the program of the Study Section major emphasis has been placed upon basic research on the biology and physiology of malaria parasites. It was felt that the first duty of the Study Section was to continue those phases of the work in chemotherapy which would have been incomplete without its support. Since the chemotherapy program sponsored a series of interdependent activities beginning with the chemical synthesis of potential antimalarial drugs and ending with the clinical testing of those showing the most promise, it was decided to decrease the research activity at the synthesis level first, and to follow through the various stages (screening, toxicity, and clinical investigation) with a similar decrease in activity until the entire chemotherapy program was brought into proper focus with respect to the overall program of the Study Section. The major part of the reorientation of the malaria research sponsored by the Study Section has been accomplished during the past year.

The Study Section was aided in making this transition by the recommendations of two committees, who gave advice on the future role of the Study Section in the malaria field. From the committee reports came (1) overall recommendations for a reorientation of malaria research in the direction of basic studies on the malaria parasites, (2) specific recommendations concerning the proper emphasis to be given to the various phases of the chemotherapy program, and (3) a review of neglected fields of research in malaria. The paucity of information on the bionomics of several of the important vectors in malaria and the need for fundamental information on the parasite-mosquito and the mosquito-human relationship of many of the important species of anophelines was emphasized in this review.

Research sponsored by the Study Section during the past two years has led to considerable overall progress in the field of malaria. By the use of human volunteers and using a standardized experimental infection, it has been possible to screen new drugs against Plasmodium vivax in man. These advances have been made possible through the splendid voluntary cooperation of chemists, pharmacologists and physicians. The voluntary coordinated effort of these various groups and their willingness to convene as members of the group of Investigators in Malaria Chemotherapy in order to aid in the mutual exchange of scientific information has been a source of real encouragement to the members of the Malaria Study Section.

Through the efforts of this group of investigators the series of quinoline methanols has been carefully studied. It is doubtful if future work with this group of compounds would be fruitful. The series of 8-aminoquinolines, which was under investigation in the O.S.R.D. program, has been expanded sufficiently so that further synthetic work would seem to be unnecessary. Two new drugs in this series, pentaquine (SN 13,276) and isopentaquine (SN 13,274) have been shown to be superior to pamaquine as curative drugs in malaria. However, all three drugs must be given under close medical supervision.

At present, studies carried out under the sponsorship of the Malaria Study Section are concerned with many phases of malaria research. The various aspects of the fundamental biology of several avian malarias are being investigated by nine research teams in different parts of the United States. Two chemical-biochemical groups are investigating the products formed when known antimalarial drugs are degraded in man and monkey. Other projects are engaged in the synthesis of radioactive or isotopic "tracer" analogues of antimalarial drugs. The investigation of possible curative drugs is being carried out with P. cynomolgi in monkeys. Two field studies are just getting underway--one in Puerto Rico in which the bionomics of Anopheles albimanus will be investigated and one in Guatemala where both the effect of the newer antimalarial drugs and the bionomics of the same mosquito vector will be studied. In all of this work, emphasis is being placed upon the acquisition of fundamental knowledge. It is hoped in this way that significant advances can be made in the entire field of malaria.

B. Specific Advances

The following specific advances may be mentioned:

1. Increased knowledge of the nutritional requirements of both human and simian malaria parasites.

2. Plasmodium cynomolgi in monkeys reacts to known antimalarial drugs in a manner similar to that of P. vivax in man. In addition, fundamental information on the course of the infection with P. cynomolgi in monkeys has been obtained.

3. A factor has been discovered in hen's blood which prevents the sporozoites of the 3H2 strain of P. cathemerium from infecting a canary.

4. Important advances in correlating changes in the metabolism of P. gallinaceum with the immune responses of the host.

5. Knowledge of the action of the 8-aminoquinolines in human patients infected with P. vivax has been greatly aided by careful studies in prisoner volunteers. In this work many synthetic drugs in a series have been prepared and have been screened against the various avian and simian malarias. Two drugs of promise, pentaquine and isopentaquine, have resulted from this cooperative effort.

6. The usefulness of P. cathemerium in the canary as a screening test for curative drugs has been demonstrated.

7. The chemistry of febrifugine, an alkaloid of a Chinese plant, has been carefully studied. The elucidation of the structure of this compound may give the key to synthetic work, since it has considerable antimalarial activity.

8. Human plasmodia have been preserved by quick freezing methods. This technique will have many uses both for research workers in the field of malaria and for those scientists using malaria as a therapeutic measure.

II. RESUME OF STUDY SECTION REVIEW OF APPLICATIONS FOR RESEARCH GRANTS (January 1, 1946 to July 1, 1948)

A. Number of applications considered: 76, in amount of $1,060,786.
B. Number of applications approved: 65, in amount of $892,979., or 85.5% of applications reviewed. (29 projects.)
C. Number of applications disapproved: 11, in amount of $105,535., or 14.5% of applications reviewed.

III. RESEARCH OBJECTIVES

A. Immediate Aims and Estimate of Financial Needs for the Period July 1, 1949 to July 1, 1950

Whereas the wartime program of research sponsored by the O.S.R.D. was concerned chiefly with the chemotherapy of

malaria, the Malaria Study Section feels that now major emphasis should be placed upon basic research on the biology and physiology of malaria parasites. A review of the neglected fields of malaria investigation indicated the need for fundamental information on the bionomics of several important vectors as well as the necessity for fundamental work on the parasitology of the problem.

It is estimated that investigations sponsored by the Malaria Study Section for FY 1950 will require $350,000 to be spent as follows:

Fundamental research in biological studies on the malaria parasite, including immunological studies, research on the biochemistry and physiology of the parasite, and the development of new techniques--$100,000.

Field studies on malaria--investigations on the effectiveness of new synthetic drugs in the field, studies on the bionomics of the vector and related investigations--$100,000.

The mechanisms of drug action, including studies on the physiological distribution of antimalarial drugs, the use of drugs containing isotopic elements, the action of drugs on the biological systems of the parasite, and the degradation of such drugs in the host--$80,000.

The chemotherapy and biology of primate malaria and related studies--$70,000.

B. Long-Range Objectives and Estimate of Financial Needs for the Five-Year Period July 1, 1949 to July 1, 1954

The most important long-range objective is the improvements of methods for malaria control. Such improvements will come through basic knowledge gained in the laboratory, in the field and through the development of efficient techniques, including solution of the organizational problems related to actual control work. Another objective is the development of a curative antimalarial drug of low toxicity. It was hoped that such a drug might be found among the 8-aminoquinolines; however, extensive exploration of the many possible isomeric compounds of this series has failed to produce the desired result.

It is difficult to anticipate the direction of future research in the field of malaria. The continuation of extensive field studies of known antimalarials is very necessary, in order that knowledge of the extent of

their usefulness may be obtained. Information of this type is especially needed with respect to the newer drugs. Then, too, basic relationships such as vector-parasite, host-parasite, etc., can best be determined through field studies. It seems safe to state that a considerable portion of the annual grants of the Malaria Study Section will have to be for such investigations.

For the five year period under consideration it is anticipated that $1,900,000 will be required. This figure is based upon the assumption that the same general program outlined under IIIA. for FY 1950 is to be followed, and it includes an allowance for the increased amounts required by the field studies which the Study Section has authorized.

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METABOLISM AND ENDOCRINOLOGY STUDY SECTION

METABOLISM AND ENDOCRINOLOGY STUDY SECTION

I. PROGRESS IN RESEARCH.

A. Overall Progress.

Since its inception the Metabolism and Endocrinology Study Section has received requests for funds for many important and useful research projects from the country's outstanding investigators. Some of the grant support has gone, and is going, for research of immediate clinical application, although considerably more than half is financing much-needed basic research.

The projects supported under this program fall into three main groups as follows:

1. Endocrine - adrenal cortex, pituitary, thyroid, and sex hormones.

2. Carbohydrate metabolism - diabetes.

3. Cholesterol metabolism - arteriosclerosis.

The largest portion of support the first year went into projects which fall in group "1" above, and therefore it is this part of the program on which more progress has been made. Groups "2" and "3" follow in the order named from the standpoint of financial support and number of projects.

In the fall of 1947 a symposium on arteriosclerosis was held in New York City under the sponsorship of this Study Section. This meeting stimulated several excellent applications in this field which were favorably acted upon at the winter meeting. At this winter meeting the continuation projects largely fell in group "1" and the new projects in group "3." A second symposium was held at the winter meeting in Cleveland on "Liver Function and Liver Diseases."

B. Progress in Specific Projects.

The steroid hormones - their detection, measurement and function in bodily processes - are receiving much attention at the present, and there are several grant-supported projects on which significant progress was made during the year. For example, by the use of radiosodium, methods for the detection of small quantities of one group of the adrenal cortical steroids have been worked out and grant-supported work

has contributed toward an understanding of the role of cortical steroids in carbohydrate, potassium and sodium metabolism. Advances were also made in the detection of these steroid hormones in the urine and sweat of persons with various diseases. Progress was reported on a project seeking to synthesize new steroid-like compounds with sex and adrenocortical activity. A possible relationship of sex and adrenal cortex steroids is indicated by the observation of a grantee that the ovaries under certain conditions can maintain life in animals from which the adrenal glands have been removed. Another worker reports progress in elucidation of the problem of female sex hormone inactivation and another in measuring these hormones in women suffering from menstrual illnesses.

Perhaps the greatest single need in the steroid hormone field at the present is adequate chemical methods for the determination of these substances in body fluids and organs. Toward this end several projects were approved during the year and a beginning was reported on chemical methods for the determination of the male sex hormone in blood.

It has been known for some time that the anterior pituitary gland motivates other endocrine glands. Progress was reported on the exact action of several pituitary hormones, including important new data on at least two which have been purified. With support in part from this program, the growth hormone has been found to have an essential metabolic effect on various cells of the body and may even have to do with abnormal growth of cells such as occur in cancer.

Fetal wastage is commonly known to be relatively high among the 50,000 diabetic pregnancies each year. Grant-supported work on the cause and means of combating this loss of life progressed during the year. The maternal vascular disease which accompanies diabetes is believed to be an important cause of fetal death. Corrective hormonal treatment offers considerable possibilities for successful control, judging by work reported this year.

Other important advances of a fundamental nature were reported. These include work on pituitary-induced diabetes, carbohydrate metabolism, antagonists for insulin, insulin hypersensitivity, insulin inactivation, and effect of various chemical substances on the pancreas.

Mention should also be made of advances in diseases of the thyroid and the function of this gland in normal individuals, the relation of hormones to liver diseases, and hormones of the digestive tract and their possible role in peptic ulcer.

II. RESUMÉ OF STUDY SECTION REVIEW OF APPLICATIONS FOR RESEARCH GRANTS (January 1, 1946, to July 1, 1948).

A. Number of applications considered: 116, in amount of $1,090,674.
B. Number of applications approved: 83, in amount of $684,628, or 72.0% of applications reviewed. Represents 50 projects.
C. Number of applications disapproved: 33, in amount of $339,622, or 28.0% of applications reviewed. Percentage applies to number of applications, not funds.

III. RESEARCH OBJECTIVES.

A. Immediate Aims and Estimate of Financial Needs for the Period July 1, 1949, to July 1, 1950.

In addition to supporting the studies mentioned above, new research should be started or extended on the following subjects:

1. Treatment or means of preventing blindness among diabetics.

2. Metabolic and endocrine aspects of arteriosclerosis.

3. Role of the hormones in cancer formation.

4. Cause and a possible "cure" of diabetes.

5. More information on the cause and treatment of human infertility.

It is believed that $1,200,000 would be a reasonable estimate of the cost of research in these and other aspects of metabolism and endocrinology which could be carried out in the fiscal year 1950.

B. Long-range Objectives and Estimate of Financial Needs for the Five-year Period July 1, 1949 - July 1, 1954.

If all promising projects are supported, it is estimated that $8,400,000 will be required to finance the program for the five-year period from July 1, 1949, to July 1, 1954.

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PATHOLOGY STUDY SECTION

PATHOLOGY STUDY SECTION

I. PROGRESS IN RESEARCH.

A. Overall Progress.

Since there are special Study Sections for reviewing applications in the fields of many specific diseases, the Study Section established for making recommendations on applications in the "science pertaining to diseases" (pathology) receives largely applications in this broad field for which there is no special Study Section. For this reason the applications for grant support that have been recommended by the Pathology Study Section since the inception of the program have had a wide range.

Many of the projects being supported in this program are entirely exploratory in nature, or investigation into underlying basic principles involved in the disease process. Progress on this type of research is necessarily slow and the final outcome is, of course, frequently unpredictable. However, the Study Section feels that fundamental research or the "looking for new tools" is the wisest investment that can be made.

On the other hand, several projects receiving support are largely clinical investigations or the application of known principles and previously worked-out methods. This latter type of investigation is expected to yield, and is yielding, results of immediate importance.

B. Progress in Specific Projects.

An extensive project on the cause of rheumatic fever has been under way for more than a year. The cause of this crippling disease, particularly in children, has baffled pathologists for a long time, but some progress toward a solution to the problem has been reported by the workers supported by grant funds.

In addition, progress of varying significance has been made on the following investigations: chronic intestinal obstruction, anatomy of the veins, an analysis of experimentally-induced encephalomyelitis, causes of death in stillborn and newborn infants, bacterial endocarditis, toxemia of pregnancy, role of cholesterol in disease of the arteries, structure of abnormal nerve cells, cause of fever, relationships of kidney to high blood pressure, abnormal development of the central nervous system, interre-

lationships between diseases of the liver, kidney and heart, correlation of temperature causing skin burns with healing time.

II. RESUMÉ OF STUDY SECTION ACTIONS ON APPLICATIONS FOR RESEARCH GRANTS (January 1, 1946, to July 1, 1948).

A. Number of applications considered: 76, in amount of $819,414.
B. Number of applications approved: 57, in amount of $394,327, or 75.0% of applications reviewed. Represents 37 projects.
C. Number of applications disapproved: 19, in amount of $200,055, or 25.0% of applications reviewed. Percentage applies to number of applications, not funds.

III. RESEARCH OBJECTIVES

A. Immediate Aims and Estimate of Financial Needs for the Period July 1, 1949, to July 1, 1950.

Important new studies in addition to those mentioned above should be stimulated and supported in the fiscal year 1950. A breakdown into areas follows:

1. Infectious diseases: virus, rickettsial, bacterial, fungus, protozoal, metazoan.

2. Chemical intoxications, dietary and mineral deficiencies, and physical agents, including industrial injuries.

3. Diseases of known cause.

4. Pharmacologic histology (effect of therapeutic agents on structure and chemistry of disease processes).

5. Stimulation of development of new methods of study, such as the recently active histochemical approach.

6. Fundamental processes of growth, maturation, injury and reaction thereto, inflammation, repair, senescence, reproduction, and malignancy.

It is believed that $450,000 would be a reasonable estimate of the cost of research in these and other aspects of pathology which could be carried out in the fiscal year 1950.

B. Long-range Objectives and Estimate of Financial Needs for the Five-Year Period July 1, 1949, - July 1, 1954.

If all promising projects are supported, it is estimated that $5,000,000 will be required to finance the program for the five-year period from July 1, 1949, to July 1, 1954.

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PHARMACOLOGY STUDY SECTION

PHARMACOLOGY STUDY SECTION

I. PROGRESS IN RESEARCH.

A. Overall Progress.

In the field of drugs there are many advances of fundamental importance to science and of practical importance in the treatment of disease that can be accomplished through a Research Grants program.

The mechanism of action and the biochemical changes produced in the body by some of our most important drugs are poorly understood. Knowledge along these lines will enable the physician to employ greater skill in their use, and it will pave the way for the development of new and improved remedies.

Since the addition of Pharmacology to the group of biological sciences about 1872, the therapeutic armamentarium available to the medical and dental professions has been compeltely revolutionized and all of the changes, without important exception, have been made through the experimental laboratory. During the past decade the pace of the change has been greatly accelerated but it is now possible to foresee, on a basis of recent trends, the probable course of further advances in the near future. They can conveniently be grouped in four categories:-

1. Studies of the biochemical changes produced in cells by drugs and poisons (cellular pharmacology). These include studies of cell enzyme systems, the potential value of which has been shown by the recent dramatic success of BAL against poisoning by arsenic, mercury and cadmium. Comparable studies are under way with anesthetic, analgesic, and anticonvulsant drugs, with the view of elucidating the pattern of their effects on nerve cells. Radioactive tracer elements provide a new and potent weapon for such studies.

2. Collaboration with organic chemists in the preparation and "screening" of new compounds modified from others of established value, in the search for improved remedies. This is the approach which led to the discovery of the arsphenamines, the sulfonamides, the newer anticonvulsants (dilantin, tridione) antihistamine agents, (benadryl, pyribenzamine) antimalarials, (atabrine) and analgesics

(demerol, amidone). The presently available sulfonamides, anticonvulsants, analgesics and antihistamine agents in particular are superior to their predecessors in important respects but they still have shortcomings.

3. Studies of the toxicity of DDT, pyrethrum and other insecticides, of arsenic, selenium and other hazards of industry and agriculture and of other substances of potential therapeutic value such as blood substitutes, vitamins, synthetic diets and antibacterial agents. The last-named are of special importance because, owing to the propensity of the antibiotics and sulfonamides to elicit resistance to them on the part of the germ and sensitivity to them on the part of the patient, it is necessary to continue the search for other agents to replace those now in use. The main consideration here is toxicity rather than effectiveness: there are many effective agents but only a few that are not too toxic for successful use in man.

4. Studies aimed at better understanding of the way in which beneficial or harmful effects are produced by drugs of established value. This is essentially a form of applied physiology and is aimed at better orientation of the physician in the proper use of his drugs at the bedside. It has been responsible, more than any other single type of endeavor, for the therapeutic advances of the past 70 years. Use is made of methods available for measuring various body functions in man (cardiac output, circulation velocity, blood flow, respiration, etc.). Recently it has become possible to make quantitative measurements of cerebral blood flow and cerebral metabolic activity in man and the way has thus been opened for a study of anesthetic and stimulant drugs, as well as many others, in normal and diseased human subjects. An adaptation of the same methods makes possible quantitative estimations of coronary blood flow, cardiac metabolism and the mechanical efficiency of the haart as influenced by diesease and by drugs (digitalis, quinidine, nitrates, papaverine, coramine, aminophylline) now in use to treat heart diseases. Studies of kidney function as influenced by disease and by drugs, (diuretics, sulfonamides and agents used to delay the excretion of penicillin) are beginning with the aid of the recently devised technique of catheterization of the renal vein. Studies of lung function by means of the oximeter, nitrogen meter and other devices developed during the war, are being used in conjunction with the effects of silicosis and other industrial hazards as well as the influence of drugs.

5. Grants have been awarded in each of the above categories; they serve to illustrate the practical importance of a broad program of fundamental research in pharmacology. They are but isolated instances of a need for advancement of knowledge in the field of therapeutic agents. It is proposed to extend this approach to basic investigation of many other drugs where information is needed concerning their mode of action or their toxic effects in the body.

B. Progress in Specific Projects.

Under the category of cellular pharmacology considerable progress has been made in the mechanism of action and fate in the body of anesthetic and hypnotic agents. Studies with ether, the barbiturates, morphine, and the newer morphine substitutes (demerol, amidone) upon cell respiration and enzymatic processes are yielding valuable information on the hitherto obscure mode of their action. Biochemical changes produced by the digitalis drugs on heart muscle have been demonstrated.

In the field of development of new therapeutic agents important advances have been made in anticonvulsant drugs used in epilepsy and related disorders. Laboratory methods for testing have been devised and the underlying basis of their action studied, as a procedure for rational progress. New compounds for the treatment of allergy (anti histamines), and morphine substitutes, mentioned above, are under study. One objective is to obtain a morphine substitute that will not produce drug addiction. An enzyme has been isolated from certain bacteria that will digest fibrin, and its therapeutic application to the treatment of exudates resulting from lung infections is being made.

In the field of toxicology, projects are under way to determine the effects of D.D.T. applications to crops upon the health of live stock and the possible hazard to humans from using such crops and live stock as food. Other projects in this category include the toxicity of arsenic and selenium, factors (including diet)affecting the toxicity of the sulfonamide drugs, the toxicity of snake venoms, and the isolation and pharmacology of a poison from mussels and clams responsible for human poisoning.

In the category of obtaining a better understanding of drugs commonly in use, several important accomplishments have been made. By the use of isotope "tagging", the localization and fate in the body of the widely used barbiturate drugs have been determined. The use of new methods for studying blood flow in man has been mentioned. Veratrum has been known for years to lower blood pressure, and a project is under way to isolate the specific compounds

responsible for this action and apply them to the therapy of hypertension. Methods have been devised for the study of hormones and drugs upon the human uterus, and an attack is being made on the prevention of abortion in humans.

II. RESUME OF STUDY SECTION ON APPLICATIONS FOR RESEARCH GRANTS (January 1, 1946, to July 1, 1948).

A. Number of applications considered 104; in amount of $833,457
B. Number of applications approved 76; in amount of $565,462., or 73% of applications reviewed (Represents 47 projects)
C. Number of applications not approved 28; in amount of $195,003 or 27% of applications reviewed.

III. RESEARCH OBJECTIVES.

A. Immediate Aims and Estimate of Financial Needs for the Period July 1, 1949, to July 1, 1950.

The practical accomplishments that have been cited are sufficient justification for a continuation of the schedule as it now stands. Emphasis will be placed on basic research, for this is the type of investigation best suited to our university laboratories, and experience has shown that the greatest practical achievements stem from basic research.

It is estimated that for such investigations for the fiscal period July 1, 1949, to July 1, 1950, approximately $550,000 will be needed as follows:

Fundamental research in cellular pharmacology, mechanism of drug action, distribution, fate in the body, excretion, chemical determination in body fluids -- $250,000.

Screening and development of new compounds, with a study of their action -- $50,000.

Study of the toxicology of insecticides, potential poisons used in agriculture or industry, and toxic affects of drugs used in medicine - $100,000.

Studies aimed at a better understanding of the action of drugs of established value -- $150,000.

B. Long Range Objectives and Estimate of Financial Needs for the Five-Year Period July 1, 1949 - July 1, 1954.

Rapid advances are being made in new fields such as

radioactivity, electronics, enzymology and microbiology. New physical and chemical methods for the detection and estimation of chemical compounds in the body fluids are being perfected.

These will provide valuable tools for the advancement of research in pharmacology.

The enormous value in terms of human life of the discovery of sulfanilamide does not stop with the conquest of bacterial infections. The demonstration of its antagonism by para amino benzoic acid brought out the importance of a compound to cell physiology that had been hitherto unsuspected, and further emphasized the importance of competitive enzyme inhibition in the mechanism of action of certain drugs.

It is envisioned that the most fruitful fields for future development will include:-
Chemotherapeutic agents against bacterial protozoal and virus diseases; prophylaxis of transmissable disease through effective insecticides, rodenticides, and aerosols; advances in drug therapy of heart disease and hypertension; more effective drugs in the treatment of nervous diseases, including epilepsy, migraine, and certain mental diseases; therapeutic agents of value in diseases of the endocrine glands, particularly thyroid, adrenal and sex glands; and finally a better understanding of the mechanism of action of drugs, that will bring about the development of important new drugs and a more sucessful application of existing remedies.

It is not possible to predict in which field the greatest achievements will fall. It is most likely that they will develop from observations made in basic research. For this reason basic research should be given first place in any long range program.

For the five year period July 1, 1949 to July 1, 1954, it is anticipated that $2, 500,000 will be needed as follows:

1. Continuation of program as outlined under A. for four additional years	$2,300,000
2. Development of physical and chemical methods applicable to pharmacology	$100,000
	$100,000
	$2,500,000

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PHYSIOLOGY STUDY SECTION

June 30, 1948

PHYSIOLOGY STUDY SECTION

I. PROGRESS IN RESEARCH.

A. Overall Progress.

The applications for grant in aid that have come before this Study Section for recommendation pertain to a great variety of specific research projects. For this reason, a single concise and yet complete statement of overall progress is well-nigh impossible. To date the various projects relate to the following categories: (1) Normal and pathological anatomy and physiology of the nervous system and of muscle; (2) the physiology of respiration, metabolism, and development; (3) certain physiological aspects of endocrine function; (4) physiological studies on blood, circulation, and the distribution among tissues of water, ions, and metabolites in the body of man and animals; (5) renal function; (6) the physiology of the alimentary tract; (7) problems relating to the physiology of sex and pregnancy; and (8) other projects, including physiological studies on the formation and destruction of bone, the mechanism of the secretion of sweat, physiological aspects of enzyme action, etc.

The first category, especially those studies on the nervous system, contains a larger number of grants than does any one of the others. Particularly interesting and important results have been reported by some of these investigators. Their studies have resulted in additional information on the mechanism of nutrition, growth, regeneration, and conduction of nerve tissue, the effect of electro-shock upon learning and retention, the electroencephalographic detection of brain injury in the newborn, and the nature of the stimulation that affects the thermoregulatory centers in the brain during febrile diseases.

Space limitation precludes a detailing of the productive researches that come within the other categories. Mention should be made, however, of the fact that some of these studies involved the use of radioactive isotopes, which are becoming increasingly useful to physiologists for investigations in a wide variety of subjects.

B. Progress in Specific Projects.

Neurophysiological evidence was obtained for the existence of nerve pathways between certain structures located deeply in the brain and between these and the cerebral cortex and the fiber tracts that pass down to the spinal cord. A detailed map has been worked out for certain mammals showing the topographical relationships that exist between the

different areas of the surface of the animal's body and an inner region of the brain (the thalamus). Also, a map has been developed showing how points on the cerebral cortex are related to the cerebellar cortex. These maps represent a very important contribution to our knowledge of brain organization and no doubt will be of great value to other investigators.

Further knowledge of the character of the electric disturbances in the brain that are associated with epileptic seizures and with the expressions of rage and anger has resulted from a number of researches. This new information contributes to a deeper insight into the underlying brain mechanisms that are involved in these disturbances within the organism as well as in the abnormal choreiform and athetoid movements associated with certain brain lesions.

A number of studies are in progress on the physiology of kidney excretion. These results contribute to a better understanding of the mechanism of the renal tubule as a regulator of blood composition and of the way in which the renal mechanisms function under conditions of diuresis, acidosis, nephritis, etc. Related to these studies are others on the distribution of water and electrolytes between blood and tissues in health and disease. It is reported, for example, that the paroxysms of malaria are associated with changes in cellular permeability and in the distribution of fluid between the tissue cells and the extracellular space.

Other studies are being made on the mechanism of the secretion of sweat and on the adaptation of man to hot environments, especially in regard to sweat secretion. The relationship between the chloride of sweat and that of urine have been determined and the effect of certain drugs upon the physiological mechanism of sweat secretion are being studied.

These and the other grant-supported researches are contributing importantly to our general fund of necessary scientific knowledge.

II. RESUMÉ OF STUDY SECTION REVIEW OF APPLICATIONS FOR RESEARCH GRANTS (January 1, 1946, to July 1, 1948).

A. Number of applications considered: 154, in amount of $1,967,171.
B. Number of applications approved: 131, in amount of $1,297,889, or 85.0% of applications reviewed (represents 23 projects).
C. Number of applications disapproved: 23, in amount of $399,936, or 15.0% of applications reviewed.

III. RESEARCH OBJECTIVES.

A. Immediate Aims and Estimate of Financial Needs for the Period July 1, 1949, to July 1, 1950.

The immediate aims of this Study Section are to maintain support through favorable recommendations of those continuation projects that go on yielding worth-while results as well as to encourage and support competent research through new projects for which applications may be submitted during 1950.

A reasonable estimate based upon a projection into the future of the present budgetary trend is that the cost of this program in the area of physiology during the fiscal year 1950 will amount to $1,500,000. This includes present continuation grants and an estimated number of new grants for which applications very likely will be made for that year.

B. Long-Range Objectives and Estimate of Financial Needs for the Five-Year Period July 1, 1949, to July 1, 1954.

The long-range scientific objectives include those stated above as immediate. In addition, this Study Section hopes that it will be able to encourage and support competent research in various categories that are of importance to a proper advancement of our knowledge of the basic physiology of cells, tissues, organs, and organisms, particularly in those categories that are in special need of development. It should be emphasized that basic physiological research contributes most importantly to that background of scientific information which serves as a basis for the establishment of general principles so necessary for the improvement of clinical practice. Since this is the main purpose and contribution of much physiological research, Study Section support and encouragement of such investigations will be maintained on as broad and liberal a basis as is conducive to sound scientific advancement.

Because so many of the research projects supported by this committee are in the field of kidney function, the committee is debating the advisability of holding a symposium on this subject for grantees working in this field, as well as committee members and a few others specially interested. A similar symposium in some of the other fields where considerable sums are being spent may also be considered, as in the field of muscle diseases.

Forecasting on the basis of the present budgetary trend, the financial needs in this area for the five-year period, 1950-1954, are estimated as follows:

Year		Amount Needed
1950		$1,500,000
1951		1,800,000
1952		1,950,000
1953		2,000,000
1954		2,500,000
	Total	$9,750,000

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PUBLIC HEALTH STUDY SECTION

PUBLIC HEALTH STUDY SECTION

I. PROGRESS IN RESEARCH.

A. Overall Progress.

The Public Health Study Section was organized in September 1946, and until June 1948, was designated as the Public Health Methods Study Section. The change of name was recommended by the National Advisory Health Council on the basis that the inclusion of the word "methods" had led to confusion and limited the undertaking of many types of worthwhile studies in public health that are concerned with the Section's overall program. However, in the new designation "Public Health Study Section," the term "public health" itself, as related to studies under the Research Grants program can be broadly defined as studies in a community, a population or a selected part of a population from which will come new information of value in the maintenance of community health and the prevention and control of diseases of public health importance.

During the past year and a half since its inauguration, the Public Health Study Section has been concerned with defining its field of activities. The projects reviewed have served as the basis for discussions which resulted in the crystallization of the above broad definition of public health studies. Sixteen research projects have been activated through the Section's recommendations. These fall mainly into three principal groups of studies requiring fundamental exploration, as follows:

1. The development of health and medical services

   (a) RG 250. Nation-wide Research in Child Care to Determine Health Services Currently Available.
   (b) RG 1052. The Evaluation of the Extension of Medical Care to Understaffed Areas by a School of Medicine.
   (c) RG 1513. Study of Methods and Costs in Provision of Comprehensive Medical Care for Young Children.

2. Organization of public health services

   (a) RG 81. Library Research on Global Epidemiology.
   (b) RG 270. Quantitative method of Indexing Gingival Disease.
   (c) RG 317. Research in the Field of State and Local Health Administration.

(d) RG 388. BCG Inoculation in Early Infancy.
(e) RG 610. Costs in Public Health Nursing.
(f) RG 1003. Efficacy of Nasopharyngeal Irradiation in the Prevention of Deafness.
(g) RG 1552. Evaluation of Health Education Activities by Opinion Poll Techniques.
(h) RG 142. Fluorine and Dental Caries.
(i) RG 261. Rheumatic Fever and Rheumatic Heart Disease.
(j) RG 322. Development of Standards for Healthful Housing.

3. Fundamental growth studies

(a) RG 364. Longitudinal Studies of Child Health and Development.
(b) RG 546. The Study of the Significance of Individual Differences in growing Human Beings.
(c) RG 1039. X-ray Standards for Assessing Skeletal Development.

B. Progress in Specific Projects

The great majority of studies under this Section have not been under investigation a sufficient length of time to show measurable progress. Three projects that have progressed considerably are discussed briefly.

RG 250, "Nation-wide Research in Child Care to Determine Health Services Currently Available" under the direction of Dr. John P. Hubbard of the American Academy of Pediatrics will be completed in October 1948. It is a study to make known the nation's needs for child health services. The 48 State pediatric societies will be supplied with factual data from which they will determine the needs in their respective States, and from which they will be able to make concrete recommendations for improving and developing pediatric services. Because of the progress already made in this study the American Academy of Pediatrics has set up a committee to make recommendations for the country as a whole for meeting the health and medical care requirements of children. Thus it is evident that this study is resulting in definite action.

RG 610, "Costs in Public Health Nursing" under the direction of Elizabeth Stobo, R.N., National Organization for Public Health Nursing, will establish a method for determining the cost of public health nursing by the application of well-recognized cost

accounting procedures. The purpose of the study is to evaluate and improve public health nursing services through the proper allocation of funds. The method of cost computation will have general application in public health nursing agencies, both official and voluntary. It may also have application in public health agencies generally.

RG 546, "The Study of the Significance of Individual Differences in Growing Human Beings," directed by Dr. A. H. Washburn of the Child Research Council is a long term study of individuals as they grow from birth, through infancy and childhood into adult life. Sociological, environmental and biological factors are taken into consideration. Emphasis is being placed on the relationship between the physical characteristics and growth patterns of the individual and his own particular level of physiological functioning and pattern of psychological behavior and personality character.

II. RESUME OF STUDY SECTION REVIEW OF APPLICATIONS FOR RESEARCH GRANTS (January 1, 1946, to July 1, 1948)

A. Number of applications considered: 55, in amount of $1,135,450.
B. Number of applications approved: 26, in amount of $631,645., or 47% of applications reviewed. (Represents 16 projects)
C. Number of applications not approved: 29, in amount of $370,379., or 53% of applications reviewed.

III. RESEARCH OBJECTIVES.

A. Immediate Aims and Estimate of Financial Needs for the Period July 1, 1949, to July 1, 1950.

The immediate aim of the Public Health Study Section is to coordinate the principal types of studies now being conducted and to aid in bringing these studies to completion. On the basis of the criteria laid down by the National Advisory Health Council and in order to develop a balanced program of research, the Section will work to define more precisely the kinds of projects that belong in its province and to establish the order of importance in which problems should be studied.

It is estimated that for the fiscal year 1950, $650,000 will be needed and of this amount, approximately $220,000 will be needed for continuation projects and $430,000 for new projects.

B. Long-Range Objectives and Estimate of Financial Needs for the Five-Year Period July 1, 1949 - July 1, 1954.

The Section is in full agreement with the National Advisory Health Council that its long range objectives should be to promote studies that can result in positive action for the maintenance of community health and the prevention and control of diseases of public health importance. Projects that will accomplish this end will be of the following kinds:

1. Studies related to the extent and distribution of diseases or other public health problems in a community, population or part of a population.

2. Studies, on a community, population or group basis, in relation to the pathogenesis or dissemination of diseases of public health importance.

3. Studies of the effectiveness of prophylactic or therapeutic procedures on a community, population or group basis.

4. Studies designed to test the significance of a laboratory or clinical finding, or to test the validity of a laboratory technique, on a community, population or group basis, in relation to problems of public health importance.

5. Studies in public health methods.

   (a) Studies designed to solve organizational and administrative problems faced by health agencies in the mass application of new methods of diagnosis, prevention and control of diseases of public health importance, and in the application of new measures for the maintenance of health.

   (b) Studies designed to test or develop epidemiological methodology, or other specialized methodology used or presumably useful in public health practice.

   (c) Studies of the productivity of public health practices already in process.

   (d) Studies of the applicability of theories and hypotheses in public health organization and administration.

Based upon experience of the activities and operations of the Study Section since its inception and upon its gradual future expansion, it has been estimated that the financial requirements for the five-year period, July 1, 1949 to July 1, 1954, will be $3,750,000, or approximately $750,000 per year.

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RADIOBIOLOGY STUDY SECTION

June 30, 1948

RADIOBIOLOGY STUDY SECTION

I. PROGRESS IN RESEARCH.

A. Overall Progress.

The explosion of the atomic bomb in World War II demonstrated the destructiveness of concentrated atomic power and added a considerable area to the field of medical practice and research. Immediately confronting the physician were not only the unsolved problems of treatments for and protection against radiation injuries but also unanswered questions as to the nature of the biological effects of radiations and radioactive materials. Thus, the area of radiobiology has become of great importance to medicine in all its various aspects. Only through continued research in this area can the needed answers and solutions be attained. Recognizing that radiobiological research is being conducted under the auspices of the Navy and the Atomic Energy Commission, the Radiobiology Study Section, through its recommendations, has encouraged research that supplements rather than duplicates the investigations sponsored by the other agencies.

A serious limiting factor to progress in the radiobiology area of research has been a wide-spread lack of personnel adequately trained in the field of radioactive isotopes, as well as of other kinds of radiations. Another limiting factor is the fact that in this relatively new research area it is most frequently necessary for an investigator to devise new methods and procedures before he can go on to the collection of data. Because of the highly specialized training and experience required, many of the investigations involving radiobiological techniques are being carried on by research teams. Some of these projects are primarily radiobiological but many are researches that involve the use of radioactive isotopes chiefly as tracers. The activities of the Radiobiology Study Section consequently involve (1) the formulation of opinions on projects that are assigned to other Study Sections and which involve only or chiefly the use of tracers and (2) the formulation of recommendations for the National Advisory Health Council on projects primarily assigned to this Study Section. The number of projects for which the Study Section recommends grants to the Council is less then that for which it gives opinions to other Study Sections.

In spite of the serious personnel limitation, research in this area has shown good progress. Through studies on the effects of radiations, singly and in combination, we are

gaining a better insight into cellular and chromosomal mechanisms that are involved in mitotic cell division and genetic behavior (RG's 149, 210, 210 (S)). Other studies are yielding important new information on the various factors involved in the metabolism and composition of calcified tissues (RG 354), on the role of zinc, strontium, iron, etc., in animal metabolism (RG's 5(C), 402, 143, 671), and on the interaction and synthesis of proteins, including antibodies (RG 160(C)).

B. Progress in Specific Projects

Important studies of the effects of radiations on certain living cells are helping to shed new light on the chromosomal and genetic mechanisms involved in cell division and heredity. Treatment of the cells with near-infrared followed by x-ray irradiation increases the number of chromosomal breaks in the dividing cell and increases the mutation rate, although the near-infrared alone causes no such changes, nor do the gross chromosomal changes determine the lethals associated with them. Similar results follow treatment successively with near-infrared and nitrogen mustard, although the effects last longer and the mode of action of x-rays and nitrogen mustard evidently differ somewhat (RG 149). When near-infrared irradiation precedes irradiation with ultraviolet light, an increase in mutation rate occurs only after the peak of the mutation curve is passed; evidently the infrared lessens the mortality of the mutated cells at the higher doses. Pre-treatment with a solution of nitrogen mustard, itself ineffective, increases the effectiveness of ultraviolet light as an inducer of mutations. Evidently both near-infrared and the nitrogen mustard can sensitize genetic material in chromosomes to subsequent x-ray and chemical treatment, and pre-treatment with nitrogen mustard can sensitize to subsequent irradiation. Thus, it is possible to modify chromosomal and genetic response through the manipulation of immediate environmental factors (RG's 149, 210, 210(S)). Fundamental studies like these are most important to present and future studies of the genetic problems of man and animals.

A number of radioactive isotopes have been used in studies on the metabolism and the biological disposition of radioactive elements in the animal body. Animals treated with sodium or calcium carbonate, tagged with radiocarbon, eliminated radiocarbon through urine, feces, and expired air and showed significant concentrations of the radiocarbon in the inorganic fractions of bone and teeth. The results indicate promise of a method of using expired radiocarbon as a measure of the total dose received by an animal, which may have special use in studies of health hazard problems. Other data

have been obtained on the incorporation of radiocarbon in bone and the factors influencing this (RG 354). Studies have been made also on the metabolism and deposition of radioactive isotopes of zinc, strontium, and iron in blood cells, blood plasma and tissues of animals and man. These investigations involve the determination of normal levels of these elements and the levels associated with blood disorders. These results point to the existence of a body mechanism for the conservation and re-utilization of zinc, comparable to that recognized for iron. An important discovery is that leukemic cells contain much less zinc than do normal cells. Injected radiostrontium was found distributed throughout the skeletal system and caused leucopenia of intensity proportional to dose (RG's 5, 5(C)). In studies of thyroid function, in which radioiodine and radiocarbon were used, new evidence has strongly confirmed the wide-spread supposition that circulating thyroid hormone is chemically identical with crystalline thyroxine. Evidence was obtained as to the chemical identity of the biological precursor (diiodotyrosine) of the thyroid hormone and that goitregens, such as thiouracil, exert their anti-thyroid effect by interfering not with the uptake of iodine by the thyroid but with the conversion of the iodine to organic form (RG 402).

In a number of other project studies, information of considerable value has been collected on the uptake of radioiron by patients suffering from various disorders, the time and rate of circulation of blood in the extremities and the rate of deposition of radioactive sodium at certain tissue sites (RG 809), and the uptake of radiocopper and radiophosphorus by chick embryos (RG 143). Of particular interest from the clinical standpoint is a radiobiological study of iodinated organic compounds as contrast media for radiographic diagnosis, particularly with respect to visualization and study of the gall bladder system, the gastrointestinal canal, and the pelvis of the kidney (RG 778).

II. RESUMÉ OF STUDY SECTION REVIEW OF APPLICATIONS FOR RESEARCH GRANTS (January 1, 1946, to July 1, 1948).

A. Number of applications considered: 52, in amount of $749,472.

B. Number of applications approved: 45, in amount of $580,564, or 86.5% of applications reviewed (represents 23 projects).

C. Number of applications disapproved: 7, in amount of $87,600, or 13.5% of applications reviewed.

III. RESEARCH OBJECTIVES.

A. Immediate Aims and Estimate of Financial Needs for the Period July 1, 1949, to July 1, 1950.

The immediate aims of this Study Section are to lend support to competent research in this new field through recommendations formulated for the National Advisory Health Council and to encourage the use of radioactive isotopes as tracers by workers in other areas through the formulation of opinions to be submitted to other Study Sections. Insofar as it can legitimately do so, this Study Section wishes to lend encouragement to a more adequate training of a greater number of personnel in the specialized techniques of radiation and radiobiology.

It is estimated that $800,000 will be required to support research in the area of radiobiology during the fiscal year 1950.

B. Long-Range Objectives and Estimate of Financial Needs for the Five-Year Period July 1, 1949, to July 1, 1954.

Since the development and use of the atomic bomb there has been an increasing need for knowledge of the biological effects of radiations and radioactive isotopes. The attainment of such information has depended and continues to depend upon the development of new research apparatus and methods, as well as in the training of scientific personnel in the use of these methods. The adaptation of physical methods of radiation research to problems of biology and medicine has been necessarily slow. The determination of the more neglected areas, insofar as radiobiological research is concerned, is not simple, and this Study Section has as a part of its long-range objective a clearer delineation of these needs. The long-range objectives of this Study Section include also those stated as immediate aims, but particularly it wishes to encourage and support radiobiological research in those areas where it is most badly needed and in which radiobiological methods have not been used adequately. For example, there is at present a need for considerably more research on the effects of various types of radiation on the blood, blood cells, and hemopoietic systems of mammals and other animals and for research on procedures and treatments that might be used to alleviate the biological disturbances caused by radiations and radioactive isotopes. Particularly important is a need for development in the therapeutic uses of radiations and radioactive isotopes and for the application of tracer methods in studies of neoplasms.

III. RESEARCH OBJECTIVES.

A. Immediate Aims and Estimate of Financial Needs for the Period July 1, 1949, to July 1, 1950.

The immediate aims of this Study Section are to lend support to competent research in this new field through recommendations [illegible] for the National Advisory Health [illegible]

As times goes on it may be expected that there will be a continuous, though perhaps not extremely rapid, overall expansion of the radiobiological research carried on throughout the country. Judging from the present budgetary trend in the research grants program for radiobiological work, the following figures are estimates of financial needs for the fiscal years 1950-1954:

Year		Amount Needed
1950		$ 800,000
1951		975,000
1952		1,075,000
1953		1,120,000
1954		1,170,000
	Total	$5,140,000

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SANITATION STUDY SECTION

SANITATION STUDY SECTION

I. PROGRESS IN RESEARCH

A. Overall Progress

As knowledge of the existence of the program has become more widely known, the number of applications for research grants has increased so that during the 1948 fiscal year, 28 projects were activated as against 4 projects in 1947. Thirty-one projects have been approved for activation during the fiscal year 1949 and grantees on 8 projects which are now in operation, but which have an ending date in December 1948, will probably request continuation. Therefore, if sufficient funds are available there will be 39 active projects during 1949, exclusive of new applications which may be approved and activated in the interim.

The field of sanitation is a very broad one and it is gratifying to find that as the second year of operation ends applications have been received in most of the sanitation fields. Those approved for research grants have been in the following general fields: Atmospheric pollution, food sanitation, industrial hygiene, hygiene of housing, industrial waste treatment, insect and rodent control, sewage disposal and treatment, swimming pool sanitation, water supply and treatment, and shellfish sanitation.

B. Progress in Specific Projects

Projects now underway already have been instrumental in developing valuable information on sewage contaminated irrigation waters used on truck crops, on pathogenic bacteria on frozen foods, on atmospheric contaminants in an industrial community, on toxic algal growths in surface waters, on cyanide wastes, and on housing hygiene.

A project at the University of Colorado concerned with developing quantitative procedures for measuring intestinal pathogens and indicating organisms in irrigation water and in washings from fruits and vegetables should provide useful information needed for better control of dysentery and typhoid from irrigated vegetables and fruits.

Another project for determining the longevity and behavior of pathogenic bacteria in frozen foods has important implications because of the immense amount of food being processed by the freezing method. An attempt is being made to develop more satisfactory methods of testing for bacteria on the frozen foods, and

bacterial habits are being studied during the freezing and thawing periods and during frozen storage of foods.

A study is proceeding at the University of Cincinnati for determining the nature of contaminants in city atmospheres. This project includes the sampling of atmospheres from locations in the industrial, business, and residential sections of the city. The sampling points were also chosen with a wide range of elevations. This information should prove helpful in establishing basic criterion for the control of atmospheric contaminants that are harmful to health.

The origin of certain algae bloom which are toxic is being studied at the University of Minnesota. Several cattle have been killed by drinking the toxic lake waters and it is also a potential source of danger to people. In the same category is a study for determining a method for treatment of cyanide wastes that may find access to streams and render the water toxic.

Another study which will probably be the forerunner of other projects in the same field -- housing hygiene -- appears to be a worthy one. A man at Yale University is studying the time and temperature effects on thermal death curves of respiratory pathogens in atmospheres of low relative humidity.

The above-described projects point up the fact that research work which is vital to our well-being, and which has not been done in the past, is now being accomplished by means of the Research Grants Program.

II. RESUME OF STUDY SECTION REVIEW OF APPLICATIONS FOR RESEARCH GRANTS (January 1, 1946, to July 1, 1948).

A. Number of applications considered: 131, in amount of $1,565,100.
B. Number of applications approved: 62, in amount of $503,374, or 47.3% of applications reviewed (represents 40 projects).
C. Number of applications not approved: 69, in amount of $973,260, or 52.7% of applications reviewed.

III. RESEARCH OBJECTIVES

A. Immediate Aims and Estimate of Financial Needs for the Period July 1, 1949, to July 1, 1950

Although considerable advancement has been made in various fields of sanitation during recent years, there is still a great need for further research. This is vividly depicted by U. S. Public Health Service reports showing that during the period 1938-46 there were

2,397 epidemics, 96,722 cases, and 467 deaths due to insanitary conditions in food, milk, and milk products. In 1946 alone there were 318 outbreaks with 13,321 cases and 17 deaths.

One of the primary problems faced by the Sanitation Study Section involves questions relative to the hygiene of housing. Although available information shows that there is a considerable amount of interest in housing research, the Section has had very few applications for grants to aid investigators in carrying out studies on housing sanitation. In addition to one project dealing with air sanitation in houses which has a direct bearing on housing, two other studies on domestic sewage disposal are of primary concern to housing sanitation. However, there still remains a curious lethargy on the part of research investigators to develop fundamental research projects bearing on housing sanitation. A growing interest in the housing problem at several universities and experiment stations will undoubtedly result in increased interest during the coming year. Therefore, it is estimated that about $100,000 will be necessary for giving proper support to investigators working on housing sanitation problems during the fiscal year 1950.

Some advancement has been made in the field of food and milk sanitation but there is still a pressing need for further research in all phases of this important field. New methods of production, processing, and handling of food products are being developed daily by industry but the basic sanitation problems are not always considered. It is therefore necessary that investigators who are interested in the sanitation problems be encouraged to do this fundamental work. It is estimated that $125,000 will be necessary for giving proper support to these problems during the coming year.

Only three applications in the field of industrial hygiene and atmospheric sanitation have been approved for grants to do fundamental research. Industry is developing new chemical processes daily and in most cases very little is known about the effects of the fumes, vapors, gases, and the chemicals themselves on the people working in such an environment. Therefore, it is anticipated that several applications will be approved in this field during the coming year and that at least $100,000 will be necessary for properly supporting such projects.

Important basic studies in the water and sewage treatment fields have been started and have shown some interesting results particularly in the testing for bacterial and chemical concentrations and on growth of bacteria in irrigation waters. Several problems in design and fundamental actions in sewage treatment have shown no results yet but it is very important that the studies be continued and that additional similar studies be made if our

streams are to be protected from excessive amounts of pollution. It is estimated that $225,000 will be needed to provide support for these projects during the coming year.

Basic knowledge regarding insects and rodents is necessary because of the dangers to health by diseases such as malaria, Rocky Mountain spotted fever, typhus, etc., which are transmitted through men as intermediate hosts. This knowledge should be of material help to communicable disease control work which is being carried on quite extensively by the Public Health Service and by other health agencies. It is estimated that $75,000 will be needed for the coming year to support projects in this field.

There is a great need for a better means of controlling contamination in swimming waters and shellfish growing waters, and for developing a more suitable indicator for establishing satisfactory indices of pollution. It is estimated that $75,000 will be needed to support research projects in this field for the coming year.

The total of the above-recommended budget needs indicates that $700,000 is necessary for providing minimum support for research in sanitation during the 1950 fiscal year. The amount $700,000 is a very conservative estimate of the support needed. Nevertheless, it is felt that this amount will support all of the really worth-while projects submitted by qualified research people during this short period of time.

B. <u>Long-Range Objectives and Estimate of Financial Needs for the Five-Year Period July 1, 1949 - July 1, 1954</u>

The main objective of the Sanitation Study Section on a long-range basis is the development of basic principles of sanitation which are necessary for progress in the control of disease in man and the elimination of pollution from our lakes and streams. These principles can be developed by exploration, experimentation, and study of existing phenomena which in essence is fundamental research. This research can be accomplished both by encouraging competent investigators who have funds available and by providing Federal monetary assistance to those research workers who have worth-while ideas but do not have sufficient funds for doing the work.

It is the policy of the Sanitation Study Section to correlate research work so that unnecessary duplication is avoided and to encourage an exchange of ideas by people interested in research in order that new fields be developed. This policy is being carried forward by holding symposiums where investigators interested in the particular field of study under discussion may meet to present their findings and to exchange ideas. Also an attempt is being made to determine the most important research

needs by inviting the cooperation of associations and societies interested in the same field of endeavor.

Present information shows that many phases of food production, processing, and handling; housing hygiene; industrial hygiene; testing for and controlling contaminants and toxic substances in water; and testing for and treating sewage and industrial wastes is much in need of study by research men. These studies are very important because they will lead to better environmental conditions at reasonable or lower costs.

The estimated amount of Federal funds needed for supporting necessary research in the fields of study covered by the Sanitation Study Section for the next 5-year period is $4,000,000.

This figure has been purposely kept conservative because it is felt that many important projects can be supported from other sources such as the National Foundation for Infantile Paralysis, American Water Works Association, American Society of Civil Engineers, and similar groups. However, the annual financial needs will be slightly greater each year for the 5-year period, because the program is still relatively new and has not yet fully developed. Also, the housing hygiene, industrial hygiene, and possibly atomic energy problems which have received only limited attention in the past and which have obtained very little assistance from the Research Grants Program are in need of additional assistance.

The Sanitation Study Section feels that the amount of funds suggested above would represent an extremely worth-while investiment by the Federal Government.

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SURGERY STUDY SECTION

SURGERY STUDY SECTION

I. PROGRESS IN RESEARCH

A. Overall Progress.

Since the first meeting of the Surgery Study Section on November 8, 1946 the Research Grant program has had the enthusiastic endorsement of surgeons throughout the United States and applications are being received in increasing numbers. It is noteworthy that as the program becomes more mature and more widely known a greater number of well conceived, large scale projects are being submitted for consideration, which give promise of valuable results and which could not have been attempted under financial support ordinarily available at hospitals and universities.

Among the major problems which are being studied under Research Grant support and in which worthwhile progress is being made, are those of peptic ulcer and its treatment by surgery of the parasympathetic nervous system, certain pathological conditions of the heart and large vessels for which specific surgical techniques are being developed, and the longstanding problem of pre- and post-operative care especially of the aged.

B. Progress in Specific Projects.

Although little of the work has advanced to the stage of publication many worthwhile contributions have already been made by investigators who have been awarded grants. One of the outstanding achievements has been the development of a method for forming a new blood supply to the heart which will allow normal cardiac function even when the coronary artery is completely occluded. This work was originally performed on experimental animals but the methods are now being applied to human patients and may ultimately prove of specific value in the treatment of coronary heart disease. Encouraging progress has also been made in the development of a pump oxygenator to replace the human heart and lungs for brief periods. If this is successful it will make possible the application of surgical methods to lesions inside the heart. A successful method has been devised for the placement of artificial heart valves in the hearts of animals to replace damaged aortic leaflets.

These artificial valves provide normal physiological function and may be of application in the treatment of certain types of cardiac disease in the human. Progress has been made on the determination of the best methods of post-operative patient care in order that post-operative mortality may be decreased and the length of convalescence shortened. These studies have already provided important

information concerning the metabolism of convalescence. Encouraging reports have also come from work on the problem of revascularization of the extremities after severance of the larger arteries. These studies may prove of especial value in the treatment of traumatic injuries.

II. RESUME OF STUDY SECTION REVIEW OF APPLICATIONS FOR RESEARCH GRANTS (January 1, 1946, to July 1, 1948).

A. Number of applications considered: 55, in amount of $594,901.
B. Number of applications approved: 45, in amount of $423,226, or 82% of applications reviewed. (Represents 28 projects)
C. Number of applications disapproved: 10, in amount of $121,164, or 18% of applications reviewed.

III. RESEARCH OBJECTIVES

A. Immediate Aims and Estimate of Financial Needs for the Period July 1, 1949, to July 1, 1950.

Important studies in a number of fields in addition to those mentioned in Section I should be stimulated and supported in fiscal year 1950.

1. Most post-operative deaths fall into categories that are probably avoidable. Research alone can guide us here. Specifically, information is needed concerning shock, heart and lung complications, infection, anesthesia, and wound healing. There is reason to believe that complications and death ratio with some anesthetic agents may be ten times higher than with other agents. No accurate data are available as to what these ratios actually are, even in the case of old, well-established agents. Safe guidance in anesthesia will not be possible until this matter is studied.

2. The development of new surgical procedures is needed for the solution of old problems of great importance to the public health in cancer, heart disease, high blood pressure, kidney and liver disease, stomach ulcers, tuberculosis. Three out of four deaths in this country are from cardiovascular disease. Up to the present time, surgical treatment has largely been denied this group. With proper surgical research, we can look forward to surgical methods for treatment of these problems.

3. More people are living to old age; therefore more of the aged will require surgery. Research must develop safe methods for reducing the hazard of surgery in this age group.

Other important problems urgently requiring large scale definitive research are:

a) Cardiovascular surgery including sympathectomy
b) Peptic Ulcer
c) Hyperthyroidism
d) Metabolic dyscrasias associated with surgery, including the problems of water and mineral balance and resuscitation
e) Blood transfusion and blood substitutes especially as related to cardiac failure
f) Toxicity associated with small air-tight oxygen masks
g) Cardiac failure in relation to surgery

It is believed that $500,000 would be a reasonable estimate of the cost of research in these and other surgical fields which could be carried out in fiscal year 1950.

B. Long-range objectives and estimate of financial needs for the 5-year period July 1, 1949 - July 1, 1954

Definitive work on the problems outlined in Subsection A is in itself a long-range project, and in most cases would require from 2-5 years or longer. It is quite probable that the annual expenditure, if all promising projects are supported, will rise to a minimum of $700,000 per year by July 1, 1954.

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SYPHILIS STUDY SECTION

I. Progress in Research Under the Syphilis Study Section Program

A. Overall Progress

Since the inception of the Syphilis Study Section's program, emphasis has been placed upon fundamental studies of the bacteriology, immunology and biology of syphilis and of the other venereal diseases in animals and in man. This emphasis is paramount because, in the opinion of the Study Section, experience to date has indicated that the control of venereal disease by the treatment of infected persons, and on the basis of past methods, seems rather likely to result in only a very gradual reduction in incidence over a long period of time. The Study Section believes that the major reason for this is the lack of fundamental knowledge in many important fields.

In addition to more fundamental problems, clinicians and research workers in this field have been deeply interested during the past few years in the application of penicillin in the treatment of syphilis. Since the program began, there has been in progress a nation-wide study of penicillin in syphilis. By pooling their resources, the cooperating clinics have amassed a vast amount of data by which penicillin in being thoroughly evaluated. To date, some 25,000 patients with early syphilis, approximately 2,000 pregnant syphilitic women, 500 syphilitic infants, nearly 4,000 patients with neuro-syphilis and several hundred additional patients with various other types of late syphilis have been treated by clinics participating in the large scale clinical experiment.

For the past year there has been in progress in nine cooperating clinics a volunteer study of the effect in early syphilis of penicillin administered in absorption-delaying media for the purpose of evaluating an ambulatory method of treatment. This study has been carried on without the expenditure of funds by the Division of Research Grants and Fellowships and with penicillin supplied to the Study Section through the courtesy of the pharmaceutical industry.

B. Progress in Specific Projects

Many of the outstanding results of the Syphilis Study Section's program were reported at a symposium held on April 8-9, 1948. The titles of the papers read at this symposium give an excellent indication of the scope of the program. Included were reports on experimental syphilis, serologic tests for syphilis,

early syphilis, the Jarisch-Herxheimer reaction, gonorrhea, neurosyphilis, primary optic atrophy, miscellaneous manifestations of syphilis, other venereal diseases and pharmacology and experimental therapeutics.

The highlights of the Symposium were:

(a) Reports by Magnuson (RG 9), Turner (RG 174), Frazier (RG 899), and Rosahn (RG 35), on experimental syphilis.

(b) Reports by Merrell and Rider (RG 32), of the most recent compilations of data from the clinics cooperating in the nation-wide penicillin study.

(c) Reports by Stokes (RG 13), Dattner (RG 14), Solomon (RG 68) and Curtis (RG 37), on therapeutic results with penicillin and penicillin combined with malaria in the several forms of neurosyphilis.

II. Resumé of Study Section Actions on Applications for Research Grants Since Inception of Program on January 1, 1946, to July 1, 1948.

A. Number of applications considered: 169. Amount: $1,948,231
B. Number of applications approved: 145.* Amount: $1,248,629(86%)
C. Number of applications not approved: 24. Amount: $699,602(14%)
* Represents 55 projects

III. Research Objectives

A. Immediate Aims and Estimate of Financial Needs for the Period July 1, 1949, to July 1, 1950.

The interest of the Study Section presently and for the immediate future is centered on fundamental studies of the bacteriology, immunology and biology of syphilis and of other venereal diseases.

Regarding the nation-wide penicillin study, it is the concensus of the Study Section that:

(1) As of July 1, 1948, the treatment of additional patients with any stage of syphilitic infection and with the aid of funds furnished by the Division of Research Grants and Fellowships, should be discontinued. (The treatment of patients with early syphilis was discontinued except on a volunteer basis as of July 1, 1947). Two exceptions to this ruling were noted:

(a) Proposals for grants for the treatment of certain phases of syphilitic infection might continue to be entertained on a limited scale if, in the opinion of the Study Section, such proposals give promise of added knowledge not already available, as for example, in the field of cardiovascular syphilis.

(b) Facilities should continue to be available in one or more clinics with appropriate laboratory facilities for the screening of any penicillin compounds, e.g., procaine, aluminum, beryllium or other new penicillins, or other new antibiotic agents of promise in syphilis or other venereal diseases.

Estimate of Financial Needs for the Period July 1, 1949, to July 1, 1940: $800,000.

B. Long Range Objectives and Estimate of Financial Needs for the 5 Year Period: July 1, 1949, to July 1, 1954.

Many of the problems of syphilology remain unsolved because virulent *Treponema pallidum* cannot be cultivated on artificial media. The Study Section will continue to view favorably projects that offer a reasonable prospect of solution to this problem. Basic studies in the biology of syphilitic infection also will be encouraged.

The immediate plans for the study of penicillin in syphilis are stated above. With respect to the continued follow-up of patients already treated, the Study Section felt that this was of importance in order to provide further information concerning the effect of various treatment systems, to aid in the differentiation between reinfection and relapse, to determine the validity of prolonged seronegativity as a criterion of cure and to elucidate further other important biologic problems dealing with syphilitic infection in man. On the other hand, the Study Section was convinced that a definite termination date, even to the follow-up study of patients already treated, should now be set. It was therefore agreed:

(a) As to early syphilis, that participating clinics would be requested to continue to follow and to report to the Central Statistical Unit all patients with early syphilis so far treated for a two-year period beginning July 1, 1948, and terminating June 30, 1950. At the latter date the study of penicillin in the treatment of early syphilis is to be regarded as completely concluded.

(b) As to neurosyphilis and certain other forms of late syphilis, all patients treated up to June 30, 1947, should continue to be followed for a minimum period of five years, i.e., until June 30, 1953.

(c) Corollary to these decisions, it was felt that financial support for the Central Statistical Unit (RG 32) should continue for at least one year following complete termination of the early syphilis study, i.e., until June 30, 1951.

Estimate of Financial Needs:

The Syphilis Study Section has endeavored by questionnaires to obtain from present grantees and prospective applicants for grants, their estimates of future financial needs. To the total of their estimates has been added $100,000 each year to cover new applications not at present visualized.

July 1, 1949, to June 30, 1950 -	$800,000
July 1, 1950, to June 30, 1951 -	775,000
July 1, 1951, to June 30, 1952 -	700,000
July 1, 1952, to June 30, 1953 -	700,000
July 1, 1953, to June 30, 1954 -	700,000
	$3,675,000

In an effort to be more specific regarding the work contemplated for the future, the Study Section has made an attempt to establish tentative category percentages as follows:

1.	Fundamental studies in the bacteriology, immunity and biology of syphilis in animals and man	50%
2.	Fundamental studies in the bacteriology, immunology and biology of gonorrhea and the minor venereal diseases	8%
3.	Applied clinical and epidemiological studies in syphilis	18%
4.	Applied therapeutic studies in syphilis	18%
5.	Applied clinical, epidemiological and therapeutical studies in gonorrhea and the minor venereal diseases	2%
6.	Biostatistical service	4%

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TROPICAL DISEASES STUDY SECTION

I. Progress in Research Under the Tropical Diseases Study Section Program

A. Overall Progress

In the earlier days of our nation, we fortunately were isolated by two oceans from a large part of the world. Our economy was not dependent, as it is today, on exports. As our agriculture has expanded and our country become more and more industrialized, our economic structure has become dependent on foreign trade. Technological and scientific developments have resulted in rapid transportation both on sea and in the air. We are no longer isolated politically, economically or physically. We are even less isolated from the standpoint of exotic diseases of the tropics, because such diseases recognize no political, economic or social barriers. Yellow fever in South America and Africa; cholera, plague and dysentery in India and China, and malaria in all the tropical and subtropical countries are of direct consequence to the commerce of our nation and to our national health and welfare.

Prior to World War II, most of the research on tropical diseases was done for us by the British and Germans, and if the results of their research had not been available to us, we should have been in a most desperate situation in prosecuting the recent World War. We would have been without atabrine, without DDT and without the sulfonamide drugs. Neither England nor Germany is now in a position to take the leadership in research on tropical diseases, and it is imperative, therefore, that we do our own studies on the problems of the tropics in order to insure our economic, military and health security. Money spent on research in tropical diseases should be regarded as an investment in the maintenance of our social and economic systems.

Since the inauguration of the Tropical Diseases Study Section, twenty-five research projects have been activated in this field. Studies have been made in 15 States and in five foreign countries (Guatemala, Australia, Japan, Nigeria, and Costa Rica). The projects have been concerned primarily with two important problems, amoebiasis and schistosomiasis; and in these conditions the most significant advances have been made. Amoebiasis is considered to be a problem of immediate practical concern, since this condition is endemic throughout the United States. Schistosomiasis occurs in American dependencies (Puerto Rico) and in areas occupied by American military personnel (Japan). Other studies have been concerned with onchocerciasis, toxoplasmosis, African sleeping sickness, filariasis, akiri and mosquito vectors.

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[illegible]

1. [illegible]

A. [illegible]

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[illegible]

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B. Progress in Specific Projects

The highlights of the Tropical Diseases program are considered to be certain significant developments in the diseases amoebiasis, schistosomiasis and onchocerciasis.

(1) Amoebiasis. On January 12, 1948, the Study Section held a panel discussion on amoebiasis. At this time, progress reports of outstanding developments were made. The titles of these papers give an excellent indication of the significance of this work:

"Possible Determinants of the Pathogenicity of Endamoeba Histolytica.

1. A Study of the Bacterial Associates and Their Susceptibility to Antibiotics" -- Dr. Faust (RG 43).

"The Antigenic Constitution of Endamoeba Histolytica" -- Dr. DeLamater (RG 355).

"Physiological Characteristics of Human Intestinal Amoebae" -- Dr. Balamuth (RG 993).

"Amoebiasis: Requirements for Growth and Control of Endamoeba Histolytica in Vitro and in Vivo" -- Drs. Johnstone and Hausen (RG 719).

"Some Aspects of Experimental Design in Cultural Studies of Entozoic Amoebae" -- Dr. Griffin (RG 787).

(2) Schistosomiasis. Several groups of workers have been actively engaged in problems relating to the chemotherapy of schistosomiasis. The work of Welch (RG 334), Beiter and Wright (RG 311), and of DeGraff (RG 360), has resulted in the screening of several hundreds of potentially effective chemotherapeutic agents. Several new compounds of considerable promise have been developed.

The studies of Meleney (RG 385), on the biology of schistosomiasis are of fundamental importance. These studies include: Comparison of several types of schistosome infections in experimental animals, including suitability of hosts, migration of young worms and histopathology; effects of chemotherapy; serologic studies; and cross infections with various types of schistosomiasis.

(3) Onchocerciasis. This disease is an important public health problem in Southern Mexico and parts of Guatemala. The

Pan-American Highway will traverse highly endemic areas of onchocerciasis, and the traffic upon the highway no doubt will influence the dissemination of the disease. The studies carried on under RG 158 are adding considerably to our knowledge of the pathology, transmission, and control of this condition.

II. Resumé of Study Section Actions on Applications for Research Grants Since Inception of Program on January 1, 1946, to July 1, 1948.

A. Number of applications considered: 60. Amount: $738,620
B. Number of applications approved: 46*. Amount: $592,438 (77%)
C. Number of applications not approved: 14. Amount: $146,182. (23%)

* Represents 25 projects

III. Research Objectives

There is urgent need to expand studies currently going on to include others in such subjects as: Tropical physiology and nutrition; other parasitic diseases such as trypanosomiasis; tropical diseases of virus and rickettsial origin such as scrub typhus and the various encephalitides; diseases of bacterial origin such as plague, cholera and diarrheas and dysenteries. Research is also needed on insecticides, larvicides and repellents.

A. Immediate Aims and Estimate of Financial Needs for the Period July 1, 1949, to July 1, 1950.

The immediate aims of the Tropical Diseases Study Section are to carry through to completion the current projects, and to stimulate new projects along the lines indicated above. For the fiscal year 1950, an extremely conservative estimate of funds needed would be $400,000. Of this, approximately $288,000 would be for continuation of studies now being conducted, and $112,000 for new projects.

B. Long Range Objectives and Estimate of Financial Needs for the Five-Year Period: July 1, 1949, to July 1, 1954.

It is anticipated that the program of the Tropical Diseases Study Section will be a gradually expanding one. The number of laboratories equipped to study certain of the tropical diseases is limited, but it is sincerely to be hoped that other groups will become interested in this field.

A reasonable estimate of the financial requirements for the five-year period July 1, 1949, to July 1, 1954, would be as follows:

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[illegible]

[illegible]

July 1, 1949, to June 30, 1950	-	$400,000
July 1, 1950, to June 30, 1951	-	425,000
July 1, 1951, to June 30, 1952	-	450,000
July 1, 1952, to June 30, 1953	-	475,000
July 1, 1953, to June 30, 1954	-	500,000
Total		$2,250,000

TUBERCULOSIS STUDY SECTION

July 1, 1948

TUBERCULOSIS STUDY SECTION

I. PROGRESS IN RESEARCH

A. Overall Progress

In broad general terms the progress of the work of the Study Section may be outlined in 6 main categories:

1. Organization of the immediate program. This has consisted in the blocking out of major areas of research for which the funds of the Section would be used, in the appointment of a Steering Committee, and several subcommittees, to consider details of operation of specific projects, in the selection of technical experts to serve as consultants for the over-all program, and in the review, evaluation, and disposition of a large number of applications for grants.

2. Cooperative clinical projects. The Tuberculosis Study Section originally came into being because of the sudden need to determine the value scientifically of the initially-promising drug, streptomycin, as a therapeutic agent in tuberculosis. In recognition of this immediate need the Study Section agreed to expend the major part of its available resources at first in carefully-planned and controlled clinical studies to define in practical terms both the effectiveness and the limitations of the drug. Such an objective necessarily involved large-scale cooperative, clinical projects. Although the greatest emphasis has been on pulmonary tuberculosis, other projects have been developed to deal with the wide variety of other manifestations of the disease. In all of the cooperative projects a number of clinical investigators, in different parts of the country, collaborate in the collection of uniform clinical observations on the treatment of selected patients in their own sanatoria or hospitals. Investigators proceed according to a carefully-designed protocol worked out by the Study Section, so that observations from different places are comparable and large enough for statistical analysis. Also, each major project includes a "control" group (or a group on a different treatment regimen), chosen by random selection, in order to determine both the basic effectiveness of an empirical standard streptomycin therapy and of variation in that standard. The following are included in the present program:

(a) Pulmonary "Control" Study

The objective of this project is the basic evaluation of streptomycin in the treatment of pulmonary tuberculosis. The program involves comparison of the course of the disease in patients given streptomycin and any other conventional therapy with that in other patients receiving other therapy but without streptomycin. Eight clinical investigators, operating under a standard protocol, are collaborating in the project and it is anticipated that 700-800 cases of pulmonary tuberculosis will be studied. At the close of the year, nearly 400 patients were under observation and an analysis and evaluation of results were well under way.

(b) Pulmonary "Comparative Regimens" Study

The project involves the use of 4 different streptomycin, time-dosage schedules in which all patients selected for treatment are given the antibiotic. Comparison of the results for the different groups will be made to determine the most effective use of streptomycin. Six investigators are collaborating and several hundred cases are to be studied.

(c) Meningeal and Miliary Tuberculosis in Children

In tuberculosis of these types streptomycin is the only therapy which gives promise of changing the almost invariable fatal outcome. The project was planned to investigate a wide variety of different time-dosage schedules, methods of administration of the drug and the use of streptomycin combined with other antimicrobial therapy. All cases of meningitis and miliary tuberculosis brought to 5 collaborating pediatricians are being treated according to a protocol designed by the investigators themselves. It is anticipated that 200-250 cases will be included in the program.

(d) Bone and Joint Tuberculosis

Five to ten orthopedists, observing the course of tuberculosis of the skeletal system according to a carefully planned protocol, are cooperating in the project. As in the pulmonary control study, half of the cases are given streptomycin plus other conventional therapy and half receive the usual treatment without streptomycin.

(e) Genito-urinary Tuberculosis

Plans for this project are being developed. The protocol under which it will operate is nearly completed and it is expected that a large number of special experts in the field will cooperate.

From work thus far completed and other current investigation on streptomycin, it is evident, first, that the drug is effective in a measurable way in treating certain forms of tuberculosis and, second, that there are serious drawbacks in its uncontrolled use, including particularly a definite toxicity for man and an effect upon the tubercle bacilli in an infected person leading to the emergence of predominantly streptomycin-resistant tubercle bacilli. As the work progresses increasing attention is being given to means of obviating these untoward effects.

3. Central Analysis and Coordinating Office. In order to assist in the analysis and evaluation of the results of the cooperative clinical studies on streptomycin, part of the funds available to the Section were used to establish a Central Analysis and Coordinating Office.

4. Central Laboratories. One of the most significant actions of the Section was to set up 3 central laboratories to carry out the more complex technical procedures required for the cooperative clinical studies. Each clinical investigator is required to send certain specimens, and may send others, for special examination. These include material for the confirmation of diagnoses, cultures for the determination of the development of resistance to streptomycin, blood and sera for the measurement of streptomycin content, etc. In addition to furnishing the clinical investigators with carefully-controlled laboratory observations, the central laboratories conduct special research studies on laboratory methods in order to improve the technical procedures currently in use.

5. Non-clinical, laboratory and field projects. In addition to the development of the cooperative , clinical, laboratory, and analyses programs, the Study Section has recommended for approval projects in bacteriology, pathology, the physiology of respiration, immunology, epidemiology, genetics, pharmacology, and other basic fields in their relation to tuberculosis. Sponsorship of investigations of basic character is expected to increase in the future.

6. Long-range program planning. In recognition of the great need for research on tuberculosis, and the present limitations of resources, the Study Section has weighed its responsibility for long-range planning of future research programs. It is apparent that the work sponsored by the Section will have great influence upon research in tuberculosis in this country; it is a primary aim of the Section to direct this influence wisely. It is recognized that the work of the Section must not tend to stifle individual freedom or initiative; at the same time, the membership of the Section fully realize that they must press energetically for the successful prosecution of those investigations which today appear most promising and fruitful.

With these principles in mind, the Study Section is preparing a long-range plan of tuberculosis research. Source material of current research is being catalogued and reviewed, subcommittees of the Study Section are studying special fields of tuberculosis with a view to further investigation, advice of experts in related fields of science is being sought, and statistical studies are under way to determine the scientific personnel needed for future programs.

II. RESUME OF STUDY SECTION REVIEW OF APPLICATIONS FOR RESEARCH GRANTS (January 1, 1946, to July 1, 1948)

A. Number of applications considered: 142, in amount of $1,462,538.

B. Number of applications approved: 94, in amount of $1,085,557., or 66.2% of applications reviewed. (Represents 58 projects.)

C. Number of applications not approved: 48, in amount of $320,341., or 33.8% of applications reviewed.

III. RESEARCH OBJECTIVES

A. Immediate Aims and Estimate of Financial Needs for the Period July 1, 1949 to July 1, 1950

For the fiscal year 1950, the Study Section believes that it should go forward with the cooperative clinical studies on tuberculosis therapy at about the same level of expenditures as during 1948-49. It can be anticipated that new antimicrobial or other agents will be available for extensive clinical evaluation and it is believed that such evaluation should follow the general pattern now in operation through the cooperative clinical studies. Since the identity of these therapeutic agents is unknown, their cost is likewise unknown. In considering estimates and budgets, therefore,

sufficient flexibility should be maintained to permit the purchase of relatively expensive drugs. It should not be necessary to change substantially the funds required for grants to clinical investigators. In line with the need to expand greatly the support of non-clinical investigators, the Study Section suggests that a total of $450,000 be reserved for such studies. In all, the Study Section estimates that $1,000,000 can be spent wisely during the fiscal year 1949-1950.

B. Long-Range Objectives and Estimate of Financial Needs for Five-Year Period July 1, 1949 - July 1, 1954

Until the work of its long-range planning group is more fully developed and a satisfactory estimate of the general wage-price structure is possible, it is not possible to estimate with reasonable accuracy the financial needs of the section for the next five years.

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VIRUS AND RICKETTSIAL STUDY SECTION

VIRUS AND RICKETTSIAL STUDY SECTION

I. PROGRESS IN RESEARCH.

A. Overall Progress.

From its first meeting on June 6, 1946, the Virus and Rickettsial Study Section has steadfastly held to two major aims: (1) to further the cause of good investigation in the general fields of viruses and rickettsiae, and (2) to encourage the training of investigators in these fields. The primary consideration which has guided the Study Section in making recommendations on grants has rested on the merits of the proposals received. There has been no effort to recommend grants on a geographical basis per se. - that is, to provide an even distribution throughout the country. On the other hand, the Study Section has been mindful from the beginning of its work of the advisability of supporting pieces of research in small institutions which are geographically remote. It has held the belief that good investigative work should be encouraged in areas where such work has not previously had an opportunity to flourish.

During its first two years of activity, just ended, the Study Section has supported certain productive research teams which had been organized during World War II for virus and rickettsial work, and which faced dismemberment in 1946 because of lack of funds. Included among these teams were one group at New York University and Bellevue Hospital in New York City engaged in a large air sterilization project, and another at the Harvard University School of Public Health, Boston, Massachusetts, working on rickettsial infections. These projects were fairly large in scope and their support amounted almost to the establishment and maintenance of a separate university department. It is improbable that in the future the Study Section will be able in a great majority of instances to finance and support a department per se, or departments organized for what might essentially be termed "routine or diagnostic work." Preference will probably be shown for the support of individual pieces of research which could not be carried out except by additional funds over and above those necessary for the running of a department.

The Study Section has watched closely the general fields of work which have been covered by the applications (both approved and disapproved) during the first two years of its existence. It has not tried to influence applicants in their choice of subjects or to suggest fields of work. Occasionally changes in methods have been suggested.

To date almost a third of the grants recommended for approval were studies on the common cold and other acute respiratory diseases, illnesses of mankind which rarely kill but which cause considerable discomfort and lost time from work. A review of the approved grants covering the two year period and including 3 grants made in the virus and rickettsial field prior to the time when the Study Section came into existence appears in Table I. No grants have been made for poliomyelitis because it is believed that the research program of the National Foundation for Infantile Paralysis adequately covers this field at present.

The Study Section has, as one special function, been asked to advise the Surgeon General of the Public Health Service with respect to collaboration by the U. S. in an international plan to control influenza, through the World Health Organization. The Study Section has recommended that this country enter into this collaborative effort, and has suggested specifically that the facilities of the Public Health Service be utilized and coordinated with those of other existing agencies in the country (Commission on Influenza of U.S. Army, and National Influenza Strain Study Center) so that a more effective program of collaboration can be devised.

B. Progress in Specific Projects.

The Study Section has been concerned as to the real efficacy of its grants program but an accurate evaluation is not yet possible. Many of the progress reports, however, have been encouraging. For example, one study on influenza has shown that the virus is infective for hamsters, lung lesions appearing in these animals after three or four passages. Lethal infections were obtained by the sixth passage and lung extracts at that time were agglutinative for red blood cells of man and the guinea pig, though not those of the chicken. Another influenza project has indicated that the administration of methionine to mice on a low protein diet greatly increases their susceptibility to the influenza virus. The antigenic relationships of various viruses has been investigated in another project by means of the Schultz-Dale in vitro technic with a view, possibly, to detecting and specifically identifying viruses in various tissues and body fluids. An investigation of the effect of phenolating various viruses has shown that their complement-fixing property is thereby greatly enhanced, although phenolation diminishes the usefulness of virus preparations as skin-testing materials.

One study is concerned with the effects on the rate of oxygen consumption in embryonated eggs when these are infected with viruses or rickettsiae and subsequently treated with various chemicals or antibiotics. Rickettsial growth has been shown in this work to be inversely proportional to the respiratory rate of the embryo cells. Para-amino-benzoic acid, which increases the respiratory rate, is markedly rickettsiostatic, whereas potassium cyanide, which lowers the oxygen consumption of eggs, enchances the growth of rickettsiae.

The several statements just given are indicative of some of the scientific results being obtained by the investigators working under the Study Section program. As time passes, and as the program expands further, the results obtained should contribute largely to the sum total of knowledge of virus and rickettsial diseases.

II. RESUME' OF STUDY SECTION REVIEW OF APPLICATIONS FOR RESEARCH GRANTS (January 1, 1946 to July 1, 1948).

A. Number of applications considered: 116, in amount of $1,424,660.
B. Number of applications approved: 79, in amount of $886,915, or 68.1% of applications reviewed. (Represents 42 projects).
C. Number of applications not approved: 37, in amount of $448,645.

III. RESEARCH OBJECTIVES.

A. Immediate Aims and Estimate of Financial Needs for the Period July 1, 1949 to July 1, 1950.

It is anticipated that support will continue to be needed for research in the same general subject areas as in past years. (see Table I) The largest single area of investigation will probably continue to be respiratory virus infections, although work on the neurotropic virus diseases should also receive substantial aid. The volume of research on general properties of viruses should increase, as should that on metabolism of both the virus and the virus-infected host. Chemotherapy will continue to deserve attention, and, if materials are found which prove efficacious in treating any virus disease, the field will immediately demand heavily increased support. It is estimated that for the year, July 1, 1949, to July 1, 1950, the sum of $550,000 should be available to support work under the Virus and Rickettsial Study Section.

B. Long-Range Objectives and Estimate of Financial Needs for the Five-Year Period July 1, 1949 - July 1, 1954.

The research aims of the Study Section continue to be those of: 1) supporting promising investigative work; and 2) the training of young men and women in the virus and rickettsial field. It is believed that the virus and rickettsial diseases represent a vigorously expanding field, the importance of which is already obvious to most of the medical, educational, and research institutions in the country. It is not the Study Section plan to attempt to force this growth in any particular direction. It is the Study Section plan to cover this field about as has been done in the past, giving priority to those applications which represent investigation rather than survey work.

It is believed that the budget for support of research in the field should continue at about the rate of $550,000 per year, with a tendency toward gradual increase.

It is difficult to estimate what new fields of research on virus and rickettsial diseases will be opened in the next five-year period. Probably the most significant potential developments lie in the therapy of these infections. The development of vaccines also represents a fruitful field for investigation in the next several years. Therefore, it is believed that over the next five-year period at least $3,000,000 should be made available for support of research recommended by the Study Section in the various aspects of virus and rickettsial diseases.

TABLE I

Distribution of approved grants by subject or field

	1946 - 47		1947 - 48			
	RG Nos.	Total	RG Nos.	Total	Total	Percentage
Respiratory Infections	11C2,163C,177C,262,262C 298,298C,308C,544,980 1024	11	11C3,262C2,298C2,308C2, 980C,1024C,1193	7	18	26
Central Nervous System Infections	237,237C,399,481	4	237C2,399C,481C,871	4	8	12
Skin Infections	172	1	1230,1308	2	3	4
Other Virus Infections	201,201C,990	3	990C,1496,1529	3	6	9
Rickettsial Infections	244,429	2	429C	1	3	4
Properties of Viruses	20CR,384,635,989	4	20C2,384C,635C,989C, 1309,1310	6	10	15
Metabolism of Agent and Host	189,189C,373,558,971	5	189C2,373C,971C,1248 1547	5	10	15
Antibiosis and Chemotherapy	256,256C	2	256C2	1	3	4
Genetics of Viruses	686	1	686C,1571	2	3	4
Air Sterilization	180	1	180CR,1174	2	3	4
					67	

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